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The American Heart Journal

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The American Heart Journal

VOL. 11 JUNE, 1936 No. 6

Original Communications

THE INADEQUACY OF THE NORMAL COLLATERAL CORONARY CIRCULATION AND THE DYNAMIC FACTORS CONCERNED IN ITS DEVELOPMENT DURING SLOW CORONARY OCCLUSION*

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IN THE preceding paper[1] evidence was presented that, in normal hearts, drugs reputed to dilate coronary vessels cause no significant improvement in the collateral blood flow to an area rendered ischemic by occlusion of its main branch. The most natural interpretation of such results would be that if such communications exist they either are too small or have little power of vasomotor response. This revives the question as to the existence of a collateral coronary supply which has interested anatomists, pathologists, physiologists, and clinicians alike for many years. A critical revaluation of available evidence is therefore opportune.

The fact that infarction is the common sequel to coronary occlusion has long seemed sufficient to convince pathologists of the terminal character of the coronary vessels. Several reports[2-7] of special instances in which complete occlusion of two coronary vessels was found post mortem without evidence of serious myocardial damage require the assumption that, at least under special conditions, adequate collateral anastomoses can develop. A review of our knowledge regarding the dynamic factors concerned in the development of a more generous collateral circulation is a second purpose of this communication.

THE CORONARY COLLATERAL SUPPLY IN NORMAL HEARTS

Within recent years, anatomical and clinicopathological studies utilizing injection methods have provided evidence that even in normal hearts communications exist between subdivisions of any large coronary ramus and (a) other coronary branches, (b) extracardiac branches, and (c) vascular and sinus channels communicating with the interiors of the right and left ventricles (Spalteholtz,[8] Campbell,[9] Wearn,[10]

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Kretz,[11] Hudson, Moritz, and Wearn.[12] The inference should not be drawn, however, that such methods necessarily demonstrate the existence of a *functional circulation* during life or that such channels are of immediate value in the emergency of a sudden coronary occlusion. Such inferences ignore the most elementary dynamics of the coronary circulation. As clearly stated by W. T. Porter[13] in 1900, "the passage of a fine injection-mass from one vascular area to another proves nothing concerning the possibility of one area receiving its blood supply from the other. Such a supply is impossible if the resistance in the communicating vessels is greater than the blood pressure in the smallest branches of the artery through which the supply must come. It is the fact of this high resistance due to the small size of the communicating branches which makes the artery *terminal.*"

Experimental evidence for a time seemed to indicate that serviceable communications exist. Pratt[14] caused a cat's heart to beat by feeding warm oxygenated blood into the right ventricular cavity. Blood which flowed from an incised vein on the surface had a dark hue indicating oxygen utilization. More recently Wiggers[15] showed that drugs limited to the right ventricular cavity of a normal cat's heart which was perfused through the aorta produces typical stimulating and depressing reactions of the left ventricle. The inference was drawn that such drugs were distributed by sinusoidal vessels against higher pressures in the coronary arteries, although a lymphatic distribution could not be excluded. Batson and Bellet[16] have presented evidence that, when injection of particulate matter incapable of passing the pulmonary capillaries causes fall of arterial and rise of right auricular pressure, particles are driven back into myocardial capillaries by venous channels.

Since the oxygen partial pressure of blood in the right heart is low and the blood is under relatively low hydrostatic pressure, it remains questionable, despite such demonstrations, whether these channels could be of much importance in providing sufficient oxygen for maintenance of contraction. Sizeable communications with the left ventricle (Wearn[10]) in which pressures are higher and the blood fully oxygenated would more probably be of service. Stella (1932), however, was unable to record any flow from the peripheral ends of coronary vessels, when all were temporarily ligated centrally, which discovery indicated that such a flow is practically nonexistent in normal hearts. At seeming variance with these conclusions were the observations of Bohning, Jochim, and Katz[17] that particulate matter injected into the ventricular cavities under conditions in which access through coronary branches was precluded, nevertheless, found its way into ventricular capillaries, as demonstrated by subsequent histological examination.

We may summarize briefly recent evidence from our own laboratory which indicates that the flow through collaterals is normally in-

significant. In the previous paper[1] we alluded to the facts that the flow from the cut end of a peripheral coronary branch is exceedingly small and that its red color suggests that the small amount of blood that does escape has not passed through the muscle tissue. Gregg, Green, and Wiggers[18] reported that the time relations of optical pressure pulses from a peripheral coronary vessel preclude the pressure rise during each systole from being due largely to transmission of pressure through collaterals, and that the peripheral coronary pressure does not rise with aortic pressure because of the transmission of greater pressure but rather because of increased action of the left ventricle. Tennant and Wiggers[19] have shown that after ligation of a main coronary vessel the blood supply is so far reduced that contraction fails within one minute and Wiggers and Green[1] found that this cannot be prevented by drugs that elevate aortic pressure or act upon collateral vessels. To this H. Green (unpublished) added still other evidence. In hearts that fibrillated the three rami were dissected out and perfused with Locke's solution under different pressures. By using the technic described in the previous paper, the rate of inflow from 180-30 mm. declining pressures was then determined in the ramus descendens anterior while pressure in the other branches was changed from 30 up to 165 mm. No alteration of flow could be detected. If collateral intercoronary communications of significant size exist, significant differences in flow should have occurred when collateral pressure was changed. In still other experiments all coronary branches except the ramus anterior descendens were perfused at a constant pressure of 80 mm., and the intramural pressure was raised from an inconsequential level of 5-10 mm. to 150 mm. Hg. The run-off from the anterior ramus descendens under a declining pressure was similarly determined at these different intraventricular pressures. Again no alteration could be detected. Such evidence points to the negligible value of collateral communications with the ventricle when counterbalancing pressures exist in the main coronary vessels.

When critically reviewed, most of the experimental evidence favors the view that from a practical aspect the coronary branches are essentially terminal; anastomoses such as exist in normal hearts apparently have no functional value.

THE DEVELOPMENT OF COLLATERAL CIRCULATIONS UNDER PATHOLOGICAL CONDITIONS

It must be emphasized, however, that these different proofs of a negligible collateral supply in normal hearts do not preclude an increase in the caliber of potential communications or the development of new systems of vessels which can furnish adequate nourishment for the myocardium under pathological circumstances.

Four sources of compensatory collateral supply are possible when a main vessel is gradually occluded, viz., (1) through development of more extensive intercoronary communications, (2) through development of extracardiac anastomoses, (3) through enlargement of arterioventricular channels, and (4) through reversal of flow from cardiac veins to blood capillaries. Gross and Kugel[20] have described the more extensive anastomoses and larger territorial distribution of the left coronary system with advancing age, which may represent a biological compensation for increasing sclerotic changes. Hudson, Moritz, and Wearn[12] have described the extensive extracardiac communications that may develop in the human heart. Beck, Tichy, and Moritz[21] have shown experimentally that such invasion from extracardial branches can be induced surgically in dogs, so that following establishment of such a supply, the main branches can be ligated without fibrillation and the muscle continues to contract when studied myographically (Bright and Tennant[22]). Robertson[23] found that when coronary vessels are slowly occluded by experimental procedures, collateral circulations occur preferentially from pericardial branches.

Factors Determining the Development of Collateral Channels.—It is commonly asserted that collateral circuits develop in regions of reduced blood supply because a need for more blood exists. *This is indeed a truism but not an explanation.* Some physical or biological mechanisms must be concerned in eventuation of the increased blood flow. The author now ventures to suggest that the slow establishment of differential pressure gradients during development of partial or complete occlusion of a main branch may distend normally useless vessels to a degree that they soon become pervious to blood. Such an initial encouragement of blood flow, though not large, would supply a source from which new vessels *that carry blood* could develop.

Since we now know the form and magnitude of the pressure changes that occur during each cycle in the left ventricle in the aorta and its branches, as well as in the peripheral end of a partially or totally occluded coronary artery, it is possible to establish the trends of flow that could occur provided adequate channels are present and to delineate the conditions under which a flow is impossible regardless of the existence of wide channels.

In Fig. 1 *A*, curve 1 represents pressure changes in the aorta and its immediate branches including the coronary vessels and curve 3, intraventricular pressure. The distance denoted by x represents isometric contraction, y, denotes systolic ejection and z denotes diastole. It is apparent that the pressure difference between the ventricular cavity and coronary branches is very slight during systolic ejection (y) and as indicated by arrows greatly in favor of a flow from the coronary arteries to the ventricular cavity during diastole (z). This directional gradient also exists during isometric contraction (x), although it becomes rapidly smaller as contraction proceeds. It is equally

obvious that at no time of the cycle does any pressure gradient exist between extracoronary or intercoronary branches; curve 1 essentially represents the pressure relations for all. Consequently it is dynamically inconceivable that any transfer of blood could occur via extracoronary anastomoses even if they were extremely large.

Let us now suppose that, as a result of gradual narrowing of a coronary branch, the pressure within this branch decreases. The pressure curve is then not only lower but changes its contour (curve 2 in Fig. 1 *B* and *C*). As indicated by arrows, the pressure gradients then become such that blood could move *from* the ventricular cavity *to* the coronary vessels during systole and in a reverse direction during diastole. As shown in Fig. 1 *C* the pressure gradients between intercoronary and extracoronary channels are favorable for a continuous

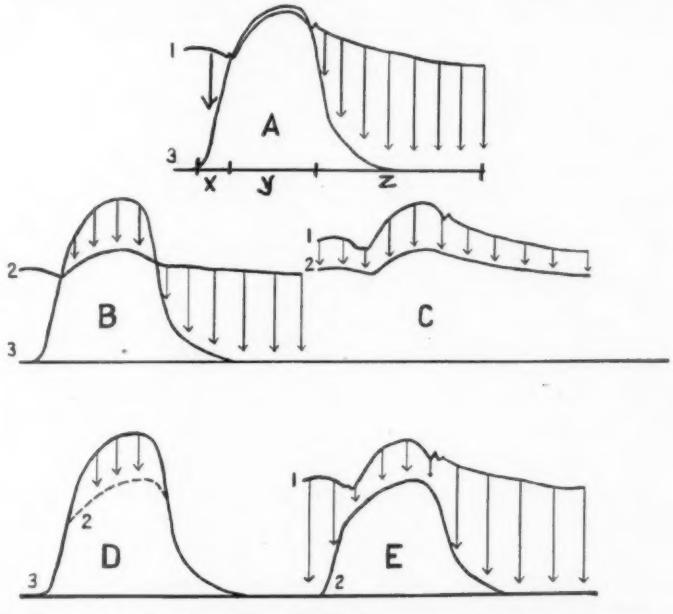

Fig. 1.—Series of curves showing differential pressures. *A*, between coronary vessels and left ventricle under normal conditions. *B*, same during partial occlusion. *C*, between partially occluded coronary and other arteries. *D*, between left ventricle and totally occluded coronary tributaries. *E*, between other arteries and coronary tributaries in occluded area. Discussion in text.

flow toward the ischemic area during systole as well as diastole. Upon general principles it might therefore be predicted that such communications would tend to develop more extensively than arterioventricular vessels, which prediction is in harmony with the experimental observation of Beck, Tichy, and Moritz[21] and of Robertson.[23] It also offers a reasonable explanation for the more extensive extracoronary communications discovered post mortem in human hearts in which some narrowing of the main arteries apparently exists.

The dynamic relations developed during complete occlusion of a coronary branch are represented by curves *D* and *E*. Curve 2 repre-

sents the contour and magnitude of pressure developed in peripheral coronary vessels, as established by optical records (Gregg, Green, and Wiggers[18]), and the upper curve 3 again represents intraventricular pressure. It is apparent that pressure gradients are again favorable for transfer of blood *from* the ventricular cavity *to* coronary arteries during systolic ejection but the great difference normally existing during diastole (curve A) is abrogated. It is therefore evident that physiological stimuli for development of such channels cannot be very potent. On the contrary, the great increase in pressure gradients between intercoronary and extracoronary branches shown in Fig. 1 *E* suggests that these vessels ought to have the better chance to develop.

Bellet, Gouley, and McMillan[24] from a microscopic study of a heart in which "the larger coronary arteries were completely occluded a short distance from their origin by tuberculous intimal involvement and by compression from a surrounding caseous tumor" concluded that the myocardium was nourished by dilatation of potential Thebesian channels. They postulate that closure of veins preceded occlusion of arteries and that arterial blood was forced to widen new channels of exit to the right auricle and ventricle. Upon subsequent closure of arteries these enlarged channels presumably nourished the myocardium from the right chambers. While their interpretation might apply to maintenance of blood supply to the right ventricle, a number of facts make such a supply to areas of the left ventricle less probable, viz., (1) right intraventricular tension does not exceed intramural tension in the left ventricle, (2) "relatively few (vascular spaces or sinusoidal channels) were present in the muscle of the left ventricle," and (3) the idea that occlusion of veins precedes closure of arteries was an inference, not a demonstrated fact. At any event such a mechanism could not operate after thrombotic occlusion which leaves the venous channels unobstructed.

SUMMARY

The evidence for and against the existence of a liberal collateral blood supply to the normal ventricular myocardium is reviewed. Evidence based on histological or injection studies is not conclusive as to the magnitude of such circulations. The volume flow through collateral vessels depends not only upon the size of communications but upon the magnitude of pressure differences. The presence of one without the other cannot result in flow. The experimental evidence is reviewed, and the conclusion is reached that in the normal heart collateral flow is extremely small and insufficient to support contractions in an area rendered ischemic by ligation of a main branch.

The existence of a negligible collateral supply in normal hearts does not preclude the enlargement of minute potential communications nor the development of new ones when a main branch is slowly occluded. In such cases, physiological mechanisms must exist to account for the

development of such circulations. The suggestion is made that, as a main branch is slowly occluded, the development of altered pressure gradients first distends normally useless channels and so furnishes a supply of blood under pressure for the newly growing vessels. The details of the probable pressure gradients are analyzed on the basis of known forces and magnitudes of the pressure variations throughout the cardiac cycle.

The essential conclusions reached are:

1. Dynamic pressure gradients are such that *normally* a transfer of blood *from* the coronary arteries *to* the ventricular cavities could occur during diastole and during the early part of isometric contractions (i.e., for perhaps 0.02 sec.) but no transfer could occur between intercoronary and coronary-extracoronary branches at any time.

2. When the size of a coronary branch is *reduced,* the pressure gradients are favorable for developing flow through intercoronary or extracoronary anastomoses throughout the cycle; and a flow *from* the ventricular cavity *to* the artery could occur during systolic ejection. During diastole the gradient of pressure favors a flow *toward* the ventricular cavity although the pressure differential is decreased in proportion to the narrowing. In other words a to-and-fro movement could occur during each heart cycle.

3. When a main coronary branch is *completely occluded,* the same pressure relations exist, except that no pressure gradient exists between coronary branches and the ventricular cavity during diastole.

4. It is improbable from dynamic considerations that reversed flow from the right heart through Thebesian veins plays any rôle in collateral supply to the left ventricle.

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THE SIGNIFICANCE OF RHEUMATIC FEVER IN THE ETIOLOGY OF CORONARY ARTERY DISEASE AND THROMBOSIS*

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IN A consideration of the causes of coronary artery disease and thrombosis it was evident that there had been some question as to the bearing of rheumatic fever on arteriosclerosis of the coronary arteries. The clinical and pathological aspects of both rheumatic and arteriosclerotic heart disease are well known. The occurrence of each is a commonplace in clinical practice. The pathological association, however, of rheumatic fever with arteriosclerotic heart disease is apparently uncommon. Reference to the older authors reveals no mention of their occurrence together, and Levine,[1] in his study of coronary thrombosis, stated that in the presence of the one lesion the other could practically be eliminated from consideration. There have been cases reported, however, in which both these types of heart disease were found simultaneously. We were interested in determining the reason, if any, other than pathological coincidence for this fact. We then analyzed the post-mortem material at Montefiore Hospital, comprising 3,264 cases during the past seventeen years, and found thirty instances, or 0.91 per cent, in which both types, coronary arteriosclerosis and rheumatic valvular disease, occurred together.

REVIEW OF LITERATURE ON RHEUMATIC CORONARY DISEASE

It is now generally accepted that active rheumatic fever causes changes in the coronary vessels of the heart as in other branches of the circulatory system. Cowan,[2] in a study of twenty-five cases of rheumatic disease, found in every instance some increase of connective tissue; and in two instances, in both of which the coronary arteries were damaged, muscular fibrosis was considerable. Though myocardial fibrosis may be due to rheumatic fever, in view of the associated coronary sclerosis, the myocardial damage was probably secondary to vascular disease. Kahn[3] is of the opinion that rheumatic fever has been inadequately stressed as a cause of coronary sclerosis, and in twenty-four out of eighty-two cases of angina pectoris he obtained a history of rheumatic fever or other acute infection. Krehl[4] described intimal changes and thickening of the walls of the smaller vessels in acute rheumatic fever, with stenosis of the lumina, hyaline changes, and round cell infiltrations of the vessel

*From the Medical Service of the Montefiore Hospital.

walls. Romberg[5] cited a case of Leyden,[6] one of thrombosis of the coronary vessels in the course of acute rheumatic fever. The former observed hyaline thrombi in medium-sized and small vessels, as well as numerous venous thromboses, periarteritis, and adventitial infiltrations. Aschoff[7] reported similar observations. Geipel[8] and, likewise, Watjen,[9] recorded endarteritic proliferation in medium- and small-sized vessels with exquisite disturbances in the internal elastic lamella. Both Kaufmann[10] and Jores[11] observed rheumatic endarteritis of the major vessels, the former also noting the lesion in the coronaries. The latter referred to Heydloff,[12] who had a case of verrucous arteritis of the carotid and innominate arteries. Raiche[13] reported a case of verrucous arteritis of the pulmonary artery. MacCallum[14] believed that coronary arteritis, arteriolar thromboses, and necroses occurred only in the severer attacks of rheumatic fever. He conjectured that extreme myocardial disability might be due to occlusion of the vessels or to their compression by adjacent Aschoff bodies. He observed focal lesions in the walls of the aorta. Rheumatic involvement of the coronary artery, aorta, celiac axis, superior mesentery, and renal arteries was described by Pappenheimer and von Glahn[15] in a male child of fifteen years. In nine fatal cases of rheumatic fever, all in patients under twenty years of age, Perry[16] described changes involving all the coats of the vessels. One of the patients, a male child fourteen years old, had anginal seizures and at necropsy a thrombus was found in the left coronary artery. Coronary artery involvement during acute rheumatic fever has been diagnosed clinically by Slater.[17, 18] The diagnosis is, however, open to question since, as pointed out by Swift and Cohn[19] and by Rothschild, Sacks, and Libman,[20] abnormal electrocardiograms frequently occur in acute rheumatic fever. Abnormal electrocardiograms have also been observed in acute pericarditis by Porte and Pardee.[21] Rothschild, Kugel, and Gross,[22] as well as White,[23] have observed coronary arteriosclerosis complicating rheumatic heart disease. Karsner and Bayless[24] recently expressed the view that rheumatism predisposes to coronary artery sclerosis, though they admit that they have not conclusively shown that coronary sclerosis is dependent upon the acute degenerative and inflammatory lesions associated with acute rheumatic fever.

ANALYSIS OF MATERIAL

Two problems have presented themselves:

1. Whether in these thirty cases the association of the coronary artery disease and the rheumatic valvular lesion was not purely coincidental.

2. Whether the coronary sclerosis represented a degenerative lesion superimposed on coronary arteries previously damaged by rheumatic fever and, therefore, predisposed to coronary sclerosis.

Age Groupings.—The ages of the patients showed a wide diversity ranging from twenty-nine to ninety-one years, with an average age of fifty-six. This figure compares closely with that of Levine[1] for nonrheumatic coronary cases, the average age of his patients being 57.8 years.

Divided into age groups the cases may be classified as follows:

	FEMALES	MALES
20-30	2	0
31-40	0	0
41-50	3	3
51-60	2	6
61-70	5	6
71-80	2	0
81 and over	1	0
	15	15

The cases are equally divided between the two sexes, though this series is too small to base any specific conclusions as to the significance of sex. It appears, nevertheless, that the combination of the two lesions appeared earlier in females. It is also noteworthy that individual longevity is gerater in the female group. The usual preponderance of males in coronary disease is not evident in this series. The reason for this may be that rheumatic valvular lesions and essential hypertension are both more common in females, the latter disease predisposing them to coronary artery selerosis.

Pathological Findings

Valvular Lesions.—There was mitral disease in 29 out of 30 cases, and in 23 mitral stenosis and insufficiency. In 6 cases there was mitral endocarditis, but in 4 of the latter no deformity of the valves. Nine had valvular disease of the mitral valve only. In 19 the mitral and aortic valves were affected. In 1, the involvement was limited to the aortic valve; in 2 others, to the mitral, aortic, and tricuspid valves. In another, in addition to the pulmonic, the mitral and aortic valves were involved. In 1 case there was also infective endocarditis of the mitral and aortic valves.

Arteriosclerotic Lesions of the Arteries.—Reference to Table I reveals the vascular lesions as well as the correlation between the vessels involved and the site of the myocardial infarction. It is noteworthy that in seventeen cases the right coronary artery was involved, and in three of these the involvement of the right was greater than that of the left. In the remaining fourteen both right and left were affected. Recently observations have come to light indicating that the right coronary artery is more commonly involved than is generally accepted. The frequency of involvement of the right coronary artery in this material is striking and raises the question as to whether the physiological work hyper-

trophy of the right ventricle secondary to mitral stenosis is a factor in sclerosis of this vessel. This question can be answered only from further study of the problem.

Cardiac Hypertrophy.—Cardiac hypertrophy was present in every case, the heart weights ranging from 380 to 900 gm. In fourteen there was known hypertension in addition to valvular lesions. In a number of cases with normal blood pressure it is possible that the coronary artery disease lowered an antecedent hypertension. Of six cases with normal blood pressure, one had severe coronary disease and aortic insufficiency, and the heart weighed 900 gm., while the other five weighed between 380 and 420 gm. In three of these there was gross evidence of cardiac hypertrophy, and in these and in the remaining two, there was microscopic hypertrophy. The weights of several hearts were not reported, but these also showed generalized cardiac hypertrophy. In all our cases, then, cardiac hypertrophy, either grossly or microscopically, was present. Whether this was caused by the valvular lesion or the hypertension, it is impossible to say.

It has been possible to correlate the heart weight and the blood pressure figures in some of these cases. Of those with hypertension the hearts in ten weighed 400 gm. or more; in one instance with aortic insufficiency and systolic and diastolic hypertension, the heart weighed 900 gm. A relatively small heart is compatible with hypertension since the heart may not increase in size although hypertension exists for many years.

Rheumatic Activity.—There were signs of rheumatic activity in sixteen of the thirty cases, constituting about 53 per cent of the material. The ages of these patients ranged from twenty-nine to seventy years. All, with the exception of 2, were forty-five years or over. The occurrence of frank carditis at these ages is unusual. Of 3 patients with old mitral lesions, one showed endocarditis of the aortic valve and the others, endocarditis of the mitral and aortic valves. Of 5 patients with mitral stenosis and insufficiency, 2 had acute endocarditis of the mitral and aortic and 3 of the mitral valve alone. Six had old double lesions of the mitral valve and aortic insufficiency. Of these, one had acute endocarditis of the aortic valve, 3 had endocarditis of the mitral valve, one, acute endocarditis of the mitral and aortic valves and another, endocarditis of the left auricle. There were 3 instances of tricuspid disease, including one of tricuspid stenosis associated with mitral stenosis and insufficiency and aortic insufficiency. Of these, one had healed endocarditis of the mitral valve, another healed endocarditis of the mitral and aortic valves, and the patient with tricuspid stenosis showed acute endocarditis of the aortic valve and healed endocarditis of the left auricle. Every patient with active rheumatic fever had frank congestive failure. Though carditis is the most significant cause of congestive

TABLE I

NO.	SEX	AGE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT CORONARY ARTERY	LEFT CORONARY ARTERY	VALVE LESIONS	RHEUMATIC ACTIVITY	ELECTROCARDIOGRAMS
1	F	45	Myomalacia				Mitral stenosis and insufficiency	Acute verrucous endocarditis of mitral and aortic valves; thrombi in right auricular appendage	
2	F	43		Fibrosis of ventricle; apical infarction		Left anterior descending occluded	Mitral stenosis and insufficiency; aortic insufficiency	Acute endocarditis of mitral valve	
3	F	29		Fibers coarser than average; increased connective tissue	Slight scattered atheromatosis		Mitral insufficiency; mitral stenosis?		
4	F	56		Posterior wall and interventricular septum extensively scarred	Marked calcification; lumina almost occluded	Marked narrowing	Mitral stenosis and insufficiency; aortic insufficiency; tricuspid valves shortened and thickened	Healed rheumatic endocarditis of mitral valve	
5	M	46	Pericarditis	Ante-mortem thrombus		Slight arteriosclerosis	Mitral stenosis and insufficiency; aortic insufficiency; tricuspid stenosis	Acute endocarditis of aortic valve; collections of cells suggestive of Aschoff bodies; healed lesion L.A., pericarditis R.V.	L.V.P. P-wave split in Leads I and II

TABLE I—CONT'D

NO.	SEX	AGE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT CORONARY ARTERY	LEFT CORONARY ARTERY	VALVE LESIONS	RHEUMATIC ACTIVITY	ELECTROCARDIOGRAMS
6	M	64		Ventricular aneurysm	Coronaries pipestem everywhere		Base of mitral valve calcified	Recent and healed endocarditis of aortic valve; fibrinopurulent pericarditis	
7	M	53		Infarct of posterior wall, fibrous streaking	Scattered atheromatosis		Mitral stenosis and insufficiency; aortic insufficiency		R.V.P., auricular fibrillation, negative T-waves all leads. Digitalis?
8	M	54	Extensive subendocardial fibrosis and hemorrhage	Slight apical thinning and fibrosis		Anterior descending, markedly narrowed, almost occluded	Mitral stenosis and insufficiency		Auricular fibrillation; unusually deep Q_3
9	F	64		Grayish streaking		Adherent granular thrombus of transverse	Mitral stenosis and insufficiency; aortic insufficiency	Healing recent endocarditis of mitral valve	
10	F	62		Large irregular patch subendocardial fibrosis	Lumen markedly narrowed at sinus; more involved than left	Lumen markedly narrowed	Calcification at base of mitral and aortic valve leaflets; thickening and rolling of cusps, fusion of commissures, and calcification of pulmonic valve		L.V.P. Auricular fibrillation; P_2 large; peak notching of QRS complexes; T_2 and T_3 inverted
11	F	29				Large branch almost completely occluded	Mitral insufficiency; mitral stenosis?	Healing endocarditis of mitral valve	Sinus rhythm

TABLE I—CONT'D

NO.	SEX	AGE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT CORONARY ARTERY	LEFT CORONARY ARTERY	VALVE LESIONS	RHEUMATIC ACTIVITY	ELECTROCARDIOGRAMS
12	F	70		Posterior wall and apex thinned; fibrosis of papillary muscles; adherent mural thrombus	Mouth markedly sclerosed; transverse and posterior descending markedly sclerosed	Anterior descending and transverse markedly sclerosed	Mitral stenosis and insufficiency, calcified vegetation on aorta above cusps	Healed recent endocarditis of mitral valve	L.V.P.
13	M	60		Mottled area in posterior wall	Red thrombus with occlusion; similar thrombus in a branch supplying posterior wall of left ventricle.	Minimal arteriosclerosis	Mitral stenosis and insufficiency; aortic insufficiency	Healed endocarditis of left auricle	Intraventricular conduction defect, prominent Q_3
14	M	58			Extensive diffuse atheromatosis, no narrowing		Mitral stenosis and insufficiency; aortic insufficiency; sclerosis of aortic valves		L.V.P. Auricular fibrillation; myocardial damage
15	F	72			Arteriosclerosis and calcification of both, no narrowing		Mitral valve shows old lesions, valve not deformed; sclerosis of aortic valve	Healed rheumatic endocarditis of mitral valve	L.V.P
16	F	60				Slight arteriosclerosis of ant. descending; other branches less involved	Mitral stenosis and insufficiency, leaflets fused		Auricular fibrillation, rapid ventricular rate; low voltage

TABLE I—CONT'D

NO.	SEX	AGE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT CORONARY ARTERY	LEFT CORONARY ARTERY	VALVE LESIONS	RHEUMATIC ACTIVITY	ELECTROCARDIOGRAMS
17	M	52		Infarct of posterior wall	Sclerosis of transv., double ostium of main stem with infective polyps overlying ostia	Narrowing of anterior descending ramus	Aortic insufficiency, subacute bacterial endocarditis of aortic valve with similar involvement of aortic leaflet of mitral valve		T_2 and T_3 inverted, high take-off of T_2 subsequently all T-waves inverted and prominent Q_3
18	M	40	Muscle fibers larger than left; parenchymal degeneration	Thinner than normal; marked parenchymal degeneration	Mouths of vessels slightly reduced by arteriosclerosis		Mitral stenosis and insufficiency; aortic insufficiency; healed vegetations on tricuspid valve	Healed endocarditis of mitral and aortic valves	R.V.P., auricular fibrillation, low voltage
19	M	67		Fibrosis of posterior wall	Arteriosclerosis of sinus of Valsalva and artery	Marked arteriosclerosis of anterior descending and transverse rami	Mitral stenosis and insufficiency; aortic insufficiency		L.V.P. Subsequently auricular fibrillation and rapid ventricular rate
20	M	62		Fibrosis of wall and septum with bulging of latter	Slight thickening of coronary arteries		Mitral stenosis and insufficiency; aortic insufficiency	Thrombotic material—early endocarditis beneath line of closure of aortic valve; fine injected vessels at base of cusps	Low voltage, subsequently complete A-V dissociation; rapid ventricular rate

TABLE I—CONT'D

NO.	SEX	AGE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT CORONARY ARTERY	LEFT CORONARY ARTERY	VALVE LESIONS	RHEUMATIC ACTIVITY	ELECTROCARDIOGRAMS
21	F	46		Infarct of wall and midportion of septum with areas of hemorrhage and fibrosis; recent infarct	Marked sclerosis; no occlusion	Marked sclerosis; recent thrombus in anterior descending ramus	Mitral stenosis and insufficiency; aortic insufficiency		R.V.P. Auricular fibrillation with rapid ventricular rate; inversion of all T-waves (digitalis?)
22	F	59	Pericarditis over apex	Infarct of anterior wall and apex	Arteriosclerosis; lumens slightly reduced		Mitral stenosis and insufficiency; aortic insufficiency	Healed and recent endocarditis of mitral valve	L.V.P. Auricular fibrillation. T_1 and T_2 inverted
23	F	61		Fibrosis of papillary muscle; infarct in midportion of lateral wall	No abnormalities	Anterior descending branch markedly sclerotic and occluded half inch from its mouth	Mesial leaflets of mitral valve thickened along edge; aortic valve rolled and thickened, chordae tendineae shortened		QRS notched and slurred, T_1 and T_2 inverted, subsequently bundle-branch and arborization block
24	M	57		Fibrosis of apex and lower fourth of septum	Arteries thickened and felt as rigid tubes with marked calcification and slight reduction of lumen most marked in left		Bicuspid aortic valve, several calcified nodules on aortic valve and slight thickening of posterior cusp		L.V.P. Premature auricular beats

TABLE I—CONT'D

NO.	SEX	AGE	RIGHT VENTRICLE	LEFT VENTRICLE	RIGHT CORONARY ARTERY	LEFT CORONARY ARTERY	VALVE LESIONS	RHEUMATIC ACTIVITY	ELECTROCARDIOGRAMS
25	M	41		Opaque areas up to 1.5 cm. of apex, posterior wall, and septum		Narrowing of lumen of anterior descending ramus, circumflex occluded	Marked stenosis of mitral valve fusion of free edge which has calcified vegetation and fusion and thickening of chordae; fusion of aortic valves with obliteration of cusps		R.V.P. Premature ventricular beats
26	F	91		Muscle fibers coarser than average	Vessels diffusely pipestem; with marked stenosis of lumina but no complete occlusion		Mitral stenosis and insufficiency; calcification of mitral valve; aortic insufficiency with calcareous deposits under surface of valve; organized thrombus attached to posterior cusp		
27	M	60		Fibrosis of anterior wall near septum	Markedly calcareous	Anterior descending ramus almost occluded	Mitral insufficiency	Endocarditis of mitral and aortic valves	
28	M	55		Scarred areas up to 4 mm.	Mouths of both narrowed by atheromata; circumflex branches of both involved		Mitral stenosis and insufficiency	Healing endocarditis of mitral and aortic valves	L.V.P. Auricular fibrillation; low voltage
29	M	63	Grayish white fibrous tissue striations		Vessels extremely sclerosed and calcified throughout their courses		Mitral stenosis and insufficiency	Old verrucae of mitral valve	
30	M	61			Coronary arteries thickened throughout, encroaching on lumina to various degrees, in some areas marked		Mitral stenosis and insufficiency; aortic insufficiency	Endocarditis of mitral and aortic valves	L.V.P. Sinus arrhythmia; premature and blocked auricular beat

failure in patients with rheumatic heart disease, the association of hypertension, coronary disease, or both, makes it impossible to determine which factor or factors produced the congestive failure.

The blood pressure figures varied a great deal, from 107 to 225 mm. of Hg systolic and from 64 to 104 diastolic. Fourteen patients had blood pressure figures of 150 or over, and nine patients, 160 systolic or higher. In 10, the diastolic pressure was 100 or over. Every patient with diastolic hypertension also had systolic hypertension. Hypertension may have been a compensatory phenomenon secondary to aortic insufficiency in some of the cases.

Angina Pectoris.—There was a history of angina pectoris in 14 cases; of these, 9 were in females and 5 in males. The preponderance of females, despite the usually greater frequence of arterial disease and angina pectoris in males, is an interesting disparity. Six had attacks of dyspnea. In 3 males the attacks occurred nocturnally; in 2 females both diurnally and nocturnally; and in one female, diurnally only. Five patients had both paroxysmal dyspnea and angina pectoris. Paroxysmal dyspnea is frequently indicative of coronary disease and is especially significant in hyposensitive individuals who give no anginal history.

In nine cases no anginal syndrome was present. Several reasons may account for this fact: (1) an inadequate history; (2) in a number of instances the clinical picture could be accounted for by one type of cardiac lesion so that no further etiological factor was sought; (3) in a number of cases another condition like pulmonary tuberculosis or malignancy overshadowed the symptoms which could have been attributed to cardiac disease; (4) in several, the vascular or valvular abnormality was so insignificant that it produced no symptoms and was purely of pathological interest; (5) other cases presented silent coronary thrombosis, and the diagnosis was made only by routine electrocardiographic examination or at the necropsy table.

Complications

Congestive Heart Failure.—Congestive failure was a striking feature in all the patients except two. One of the latter died an acute cardiac death. The factors concerned in the production of heart failure have already been referred to.

There was auricular fibrillation in 10 cases, and in all but one of these congestive heart failure was present. Eleven had sinus rhythm, and in all but one there was associated congestive failure. There were 4 cases of intraventricular conduction defect, and in all of these also there was congestive failure. It was difficult to correlate the circulatory failure with the auricular fibrillation as there were many other contributory factors.

As noted above, subacute bacterial endocarditis was present in one instance, superimposed on old rheumatic mitral and aortic valves with polyps of subacute bacterial endocarditis overhanging the double ostium of the right coronary artery.

The association of diabetes mellitus with arterial disease, and particularly coronary disease, is well known. In Levine's cases[1] the incidence was very high, about 24 per cent. Nathanson[25] in a recent study of 100 necropsies on diabetic patients found that 52.5 per cent had coronary disease, whereas only 8 per cent of nondiabetic subjects had coronary arteriosclerosis. So common is the occurrence of diabetes in arteriosclerotic heart disease that Levine believes it is second in importance only to hypertension. Whether the two diseases occur simply coincidentally in the same type of individual, as Enklewitz[26] maintains, or whether diabetes is a factor in the causation of coronary sclerosis, is still an open question, though the frequent association of the two is beyond dispute. Clinical diabetes was strikingly absent in our material. One patient had a trace of sugar in the urine on one occasion. Another had a blood sugar level of 165 mg. but no glycosuria. In the latter patient we may have been dealing with a high threshold for sugar due to arteriolar renal disease secondary to hypertension.

Electrocardiographic Findings

Electrocardiographic tracings were available in twenty-one cases. Five showed left axis deviation. Of these, Case 12 showed at necropsy extensive involvement of all the coronary arteries and an infarct of the posterior wall and apex. Cases 15 and 30 showed extensive coronary sclerosis and calcification but no infarction. Another patient (Case 5) with slight coronary sclerosis had an ante-mortem thrombus in the left ventricle. Case 24 showed extensive calcification of the coronary arteries and fibrosis of the apex and lower fourth of the septum. One patient (Case 11) with sinus rhythm had marked narrowing of a large branch of the left coronary artery but no myocardial lesion. A patient (Case 25) with right axis deviation and premature ventricular beats showed areas of fibrosis of the septum, apex, and posterior wall of the left ventricle, narrowing of the anterior descending ramus, and occlusion of the transverse branch of the left coronary artery.

Auricular fibrillation was reported in 10 cases, 5 with left, 3 with right, and 2 with no axis deviation. Of the five with left axis deviation, one case (Case 10), with inversion of the T-waves in Leads II and III and notching of the QRS complexes, showed a large patch of subendocardial fibrosis of the left ventricle and greater involvement of the right than the left coronary artery. In the second case (Case 14), in which the electrocardiogram showed also myocardial damage, the coronary arteries were diffusely atheromatous, but there was no myocardial fibrosis or infarction. The third patient (Case 19), who had also a

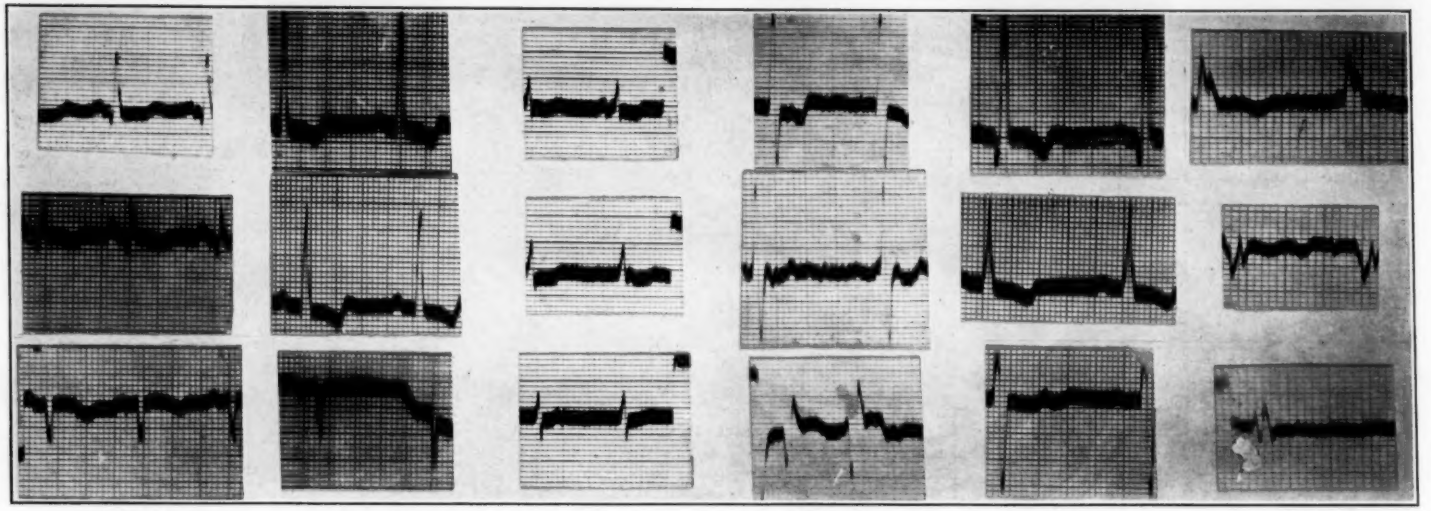

Fig. 1. Fig. 2. Fig. 3. Fig. 4. Fig. 5. Fig. 6.

Fig. 1.—Case 10. Left axis deviation large P_2, notching of QRS, inversion of T_2 and T_3. Necropsy: Marked narrowing of right coronary at sinus of Valsalva, lumen of left markedly narrowed, large irregular patch of subendocardial fibrosis in left ventricle.

Fig. 2.—Case 13. Intraventricular conduction disturbance, T_1 and T_2 negative, prominent Q_3. Necropsy: Recent thrombi of right coronary and a branch of right supplying posterior wall of left ventricle, minimal arteriosclerosis of left, mottled area in posterior wall of left ventricle.

Fig. 3.—Case 20. A-V dissociation. T_1 and T_2 partly negative. Necropsy.: Slight thickening of coronary arteries, fibrosis of left ventricle and septum.

Fig. 4.—Case 14. Left axis deviations, auricular fibrillation, partly negative T_1 and T_2, intraventricular conduction disturbance; T_1 below isoelectric line, unusually high take-off of T_3. Necropsy: Rheumatic mitral and aortic disease, extensive diffuse coronary atheromatosis, coronaries everywhere patent, no infarction.

Fig. 5.—Case 23. Left axis deviation, intraventricular disturbance, negative T_1 and T_2.

Fig. 6.—Comparison record, same case, twenty months later. Auricular fibrillation, arborization block. Necropsy: Marked sclerosis and occlusion of left anterior descending branch, fibrosis of papillary muscle and infarct of lateral wall of left ventricle.

rapid ventricular rate, at necropsy presented fibrosis of the posterior wall of the left ventricle, with marked arteriosclerosis of both right and left coronary arteries. The fourth case (Case 22) showed inversion of the T-waves in Leads I and II and had an infarct of the apex and anterior wall of the left ventricle, with diffuse coronary sclerosis conforming to the T_1 type of electrocardiogram. The fifth case (Case 28) showed also low voltage and, post mortem, diffuse scarring of the left ventricle and marked sclerosis of both coronary arteries. Of 2 patients with auricular fibrillation, with right axis deviation and inversion of the T-waves in all leads, one patient (Case 7) had an infarct of the posterior wall of the left ventricle and diffuse fibrous streaking. The second

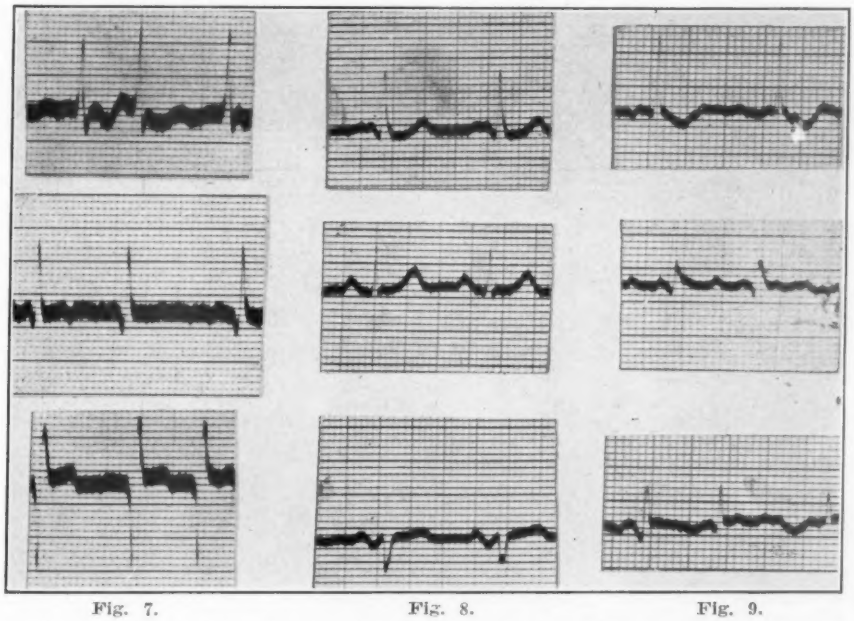

Fig. 7. Fig. 8. Fig. 9.

Fig. 7.—Case 8. Auricular fibrillation, negative T_1 and T_2, abnormal R-T transition, prominent Q_3. Necropsy: Marked narrowing of left anterior descending ramus, extensive subendocardial fibrosis and hemorrhage in right ventricle, apical thinning, and fibrosis of left ventricle.

Fig. 8.—Case still under observation. Left axis deviation with slurring of complexes.

Fig. 9.—Comparison record, same case, eight months later, following anginal seizure. Auricular fibrillation, negative T_1 and T_2, abnormal R-T transition, prominent Q_2 and Q_3.

(Case 21) with scattered coronary atheromatosis showed hemorrhage and recent infarction of the left ventricle and septum and marked arteriosclerosis of both coronary arteries. In a case of right axis deviation, auricular fibrillation and low voltage, necropsy revealed fibrosis of both ventricles and diffuse coronary arteriosclerosis. In an instance (Case 8) of auricular fibrillation with an unusually deep Q-wave in Lead III, at necropsy there were extensive subendocardial fibrosis and fresh hemorrhage in the right ventricle, apical thinning and fibrosis of

the left ventricle, and marked narrowing, with almost complete occlusion of the anterior descending branch of the left coronary. Another patient (Case 16) with auricular fibrillation, a rapid ventricular rate, and low voltage had slight arteriosclerosis of the anterior descending branch of the left coronary artery and no myocardial damage.

Marked intraventricular conduction defect occurred in 4 cases. Of these, 2 (Cases 13 and 17) with prominent Q-waves in Lead III showed posterior wall infarcts. Both had diffuse coronary arteriosclerosis with marked involvement of the right coronary artery, including recent multiple thromboses of that vessel in Case 13. Case 17 also showed abnormal R-T transition, with a high take-off of the T-wave in Lead III and inversion of all T-waves. This case presented, in addition, vegetations of subacute bacterial endocarditis overhanging the double ostium of the right coronary artery. In another case (Case 20) low voltage was followed by complete A-V dissociation and a rapid ventricular rate. The anatomical findings were fibrosis of the wall of the left ventricle and interventricular septum, with bulging of the latter and slight thickening of the coronary arteries. The electrocardiogram in Case 23 showed notching and slurring of the QRS complexes and inversion of the T-waves in Leads I and II. Subsequently, bundle-branch and arborization block developed. Post-mortem examination showed fibrosis of the apex and lower fourth of the septum, with diffuse calcification of the coronary arteries but slight reduction of the lumina, most marked on the left.

Prominent Q-waves were found in 4 cases. Three of these (Cases 8, 13, and 17) showed extensive vascular and muscular damage at necropsy. There were infarcts of the posterior wall of the left ventricle in 2 (Cases 13 and 17) and recent and old infarctions of the right ventricle and apical thinning and fibrosis of the left ventricle in the third (Case 8). The last patient, still under observation, following an anginal seizure, developed paroxysmal auricular fibrillation, a high take-off of the T-wave in Lead III, and prominent Q-waves in Leads II and III. Prominent Q-waves, especially in Lead III, have frequently been observed in coronary disease. Fenichel and Kugell[27] observed posterior wall lesions in all their patients presenting deep Q-waves in Lead III. Large Q-waves may, however, appear in advanced rheumatic heart disease, in congenital heart disease, and in disturbances of the mass relationships of heart muscle and septal displacement without coronary disease.

DISCUSSION

In our analysis we posed as our first problem the question as to whether the occurrence of arteriosclerotic and rheumatic heart disease was purely coincidental. Of the 3,264 necropsies in the records of Montefiore Hospital, the pathological association of coronary arterio-

sclerosis has been found in only thirty cases with rheumatic valvular disease. This association of the two diseases has thus been observed to be extremely rare. It is suspected that the association may have been purely coincidental. We found that either the valvular or the vascular lesion predominated and apparently was responsible for the clinical picture observed during life. There was no proved etiological relationship between the initial valvular lesion and the subsequent development of coronary arteriosclerosis.

Karsner and Bayless,[24] however, are of the belief that rheumatic fever, an inflammatory process, with an onset essentially early in life, predisposes to the premature development of coronary arteriosclerosis, a degenerative disease occurring predominantly in the middle and late periods of life. In any given case it is difficult to exclude antecedent rheumatic coronary arteritis as an etiological factor in coronary sclerosis or thrombosis. Study of our material, however, leads us to think that the two lesions may be independent and unrelated. If there were such a causal relationship, we should expect coronary arteriosclerosis with greater frequency at an earlier age in patients with rheumatic heart disease. The coronary arteries of young patients with rheumatic heart disease are usually free of arteriosclerotic changes. In short, although we cannot affirm or deny a relationship between rheumatic infection and coronary sclerosis, from the evidence before us we are inclined to believe the association is purely coincidental, and furthermore, we know that such patients live to about the same age as do the arteriosclerotic patients.

Despite the rather frequent involvement of the coronary arteries during the course of acute rheumatic fever, it has not been possible to establish such an entity on clinical grounds. To diagnose coronary disease from the electrocardiogram is unsafe. Published electrocardiograms indicating such relationship are equivocal, since similar findings may appear during acute rheumatic fever, aortic insufficiency, pericarditis, or coma. Recently attention has been called by Hochrein[28] to anginal episodes during quiescent rheumatic mitral stenosis resulting from narrowing of the coronary ostia by alterations in the mass relationships of the heart muscles. In aortic insufficiency particularly, severe anginal seizures are quite common. Schwartz[29] and, recently, Christian[30] have called attention to this phenomenon. Electrocardiograms in such cases may resemble those seen in coronary disease. These conditions have to be differentiated from rheumatic valvular disease with an accompanying coronary sclerosis. They are, however, usually sufficiently clear-cut entities to offer no difficulty in making a correct diagnosis.

Though the association of rheumatic valvular disease and coronary sclerosis is a rarity and the diagnosis is difficult, it has seemed to us that in some cases such a diagnosis might be suspected. In an individual with signs and symptoms of rheumatic heart disease who survives middle

life and later develops anginal pain, not attributable to aortic disease, active rheumatic fever, or pericarditis, the coexistence of coronary disease is to be suspected. Rare cases of angina pectoris in mitral stenosis without evidence of active rheumatic fever occur. In the absence of aortic insufficiency, an electrocardiogram may be of great help.

In two cases the diagnosis was made during life. One patient (Case 21) had hypertension, auricular fibrillation, and anginal seizures thought not to be due to rheumatic fever. The electrocardiogram showed evidence of myocardial damage, and at necropsy both coronary sclerosis and rheumatic valvular disease were present. In the other case a woman with mitral stenosis, still under observation, developed prominent Q-waves in Leads II and III following an anginal attack. In another patient who came to autopsy, the coexistence of arteriosclerotic and rheumatic heart disease might have been suspected as the patient on fluoroscopy showed a large left auricle and right ventricle, not explained by hypertension alone. While some enlargement of the right heart and left auricle occurs in hypertensive heart failure, enlargement of the right side of the heart out of proportion to congestive failure should lead to suspicion of disease of the mitral valve.

The greatest and most significant reason for the very infrequent association of rheumatic and coronary disease is that rheumatic fever appears early in life and ordinarily runs its course before the usual period of degenerative heart disease. Rheumatic patients who live beyond middle life may develop coronary sclerosis and thrombosis. If they suffer from hypertension or diabetes mellitus, they will have the predisposition to coronary sclerosis which these diseases produce. The rheumatic process appears neither to predispose to nor to prevent degeneration of the coronary arteries.

In our series coronary sclerosis was encountered twice in patients under the age of forty years. In one patient, a woman twenty-nine years old, there was minimal atheromatosis; in the other, another female of twenty-nine years, coronary disease was significant, but she had suffered from marked hypertension. Several cases are very illuminating in showing the lack of relationship between one disease and the other. A woman of seventy-two years who died of leucemia (Case 15) at necropsy showed arteriosclerosis and calcification of both coronary arteries without narrowing. The mitral valve showed old lesions of the valves without deformity. The aortic valve showed sclerosis such as is frequently encountered in advanced age as part of generalized arteriosclerosis. A woman of ninety-one years (Case 26) at necropsy showed mitral stenosis and insufficiency and aortic insufficiency, with calcification of the aortic valves. The coronary arteries were diffusely calcified, with marked stenosis of the lumina.

In several instances of severe coronary sclerosis the associated rheumatic valvular lesions were insignificant and such as are frequently

found at necropsy of individuals dying of other diseases. Similarly, in several cases of advanced rheumatic valvular disease the coincidental arteriosclerotic lesions of the coronary arteries were of no significance. In still others neither the vascular nor the valvular lesion was of more than pathological interest, and the patient had presented neither history nor findings indicative of rheumatic heart disease or coronary arteriosclerosis. Cases may be cited of rheumatic subjects at or beyond middle life, in whom coronary disease corresponds roughly to the age of the individual.

SUMMARY

Coronary thrombosis is relatively rare in patients with rheumatic valvular disease. At necropsy the coronary arteries of young patients with rheumatic heart disease showed strikingly little arteriosclerotic change.

The age period of our series corresponds to that of ordinary cases of coronary sclerosis. In this material the degenerative changes of the coronary arteries corresponded roughly to the ages of the patients.

A rheumatic subject without aortic insufficiency or active carditis who develops anginal pain may have an independent coronary arteriosclerosis. On the other hand, a patient with arteriosclerotic heart disease who shows enlargement of the right heart or the left auricle out of proportion to congestive failure may have an associated rheumatic lesion of the mitral valve.

We believe that the most significant reason for the infrequent association of rheumatic and arteriosclerotic heart disease is that rheumatic fever runs its course before the degenerative period of heart disease. Those who survive middle life, especially if they develop hypertension or diabetes mellitus, may develop arteriosclerotic heart disease. Rheumatic fever per se does not, however, appear to predispose to coronary arteriosclerosis.

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THE ARM-TO-CAROTID CIRCULATION TIME IN PROLONGED THERAPEUTIC FEVER*

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THE importance of the velocity of the blood flow in the study of the dynamics of the cardiovascular system has already been demonstrated.[1] Determinations have been made on normal individuals at rest and during exercise,[2] on patients with cardiac and thyroid disorders,[1] hypertension,[1] emphysema,[1] and anemia,[1] and following an elevation of body metabolism by means of dinitrophenol.[3] Observers have paid little attention to the effect of fever, infectious or artificial, upon the velocity of blood flow.

During the past five years the use of artificially induced therapeutic fever has increased considerably. Since this type of fever can be easily controlled, it affords an excellent opportunity to determine the effect of sustained fever upon the velocity of the blood flow.

The results of earlier experiments,[4] during which body temperature was raised and immediately lowered, have shown that artificially induced fever causes an increase in the velocity of blood flow, most marked in electric blanket fever, less so in diathermy fever, and least in fever induced by intravenous typhoid vaccine. In addition it was seen that the increase in the velocity of blood flow during diathermy fever was much more marked in a patient with syphilitic heart disease than in a patient with an apparently normal heart.

Treatment by means of therapeutic fever in this clinic necessitates the prolongation of body temperature at a level above 104° F. (rectal) from three to five hours. Repeated determinations of the velocity of blood flow on a group of patients during the fastigium of fever would enable one to note: (a) the effect of sustained fever upon the velocity of blood flow; (b) the constancy or inconstancy of these changes for nearly similar body temperatures in the same patient; and (c) the relationship between changes in the velocity of flow and other clinical findings such as pulse rate, body temperature, systolic, diastolic, and pulse pressures.

MATERIAL

Determinations of the velocity of flow were made on fifteen male patients, varying from twenty-one to fifty-three years in age, who were given fever therapy for the following disorders:

6 patients with diagnosis of general paresis
2 patients with diagnosis of congenital syphilis with interstitial keratitis

*From the Neurosyphilis Clinic of the Boston Psychopathic Hospital under the direction of Dr. Harry C. Solomon, chief of therapeutic research.

2 patients with diagnosis of primary optic atrophy
1 patient with diagnosis of tabes with gastric crisis
1 patient with diagnosis of Wassermann-fast syphilis
1 patient with diagnosis of acute gonorrheal urethritis
1 patient with diagnosis of acute gonorrheal arthritis and urethritis
1 patient with diagnosis of multiple sclerosis.

One of the patients with general paresis revealed typical findings of rheumatic mitral stenosis; a second, hypotension, bradycardia, and diminished heart sounds.

METHODS

The sodium cyanide method of Robb and Weiss[5] for the determination of the arm-to-carotid circulation time was used. From 0.55 c.c. to 0.8 c.c. of a 2 per cent solution of sodium cyanide was injected intravenously. In order to eliminate any possibility of error both the injection time and the respiratory response as obtained by means of a pneumograph were recorded on a smoked drum. A time recorder was also used, and the interval of time elapsing between the injection of the sodium cyanide into the veins at the elbow and the respiratory response was measured off and considered the arm-to-carotid circulation time. All determinations except when specified were made under basal conditions and without sedatives.

Fever was induced by means of the Kettering hypertherm,[6] an air-conditioned cabinet of from 35 per cent to 45 per cent humidity and with a standardized air velocity. Dry bulb temperatures within the cabinet range from 150 to 160° F. and the wet bulb temperature from 125 to 130° F. The patient lies within the cabinet, covered with blankets and towels, the head protruding from the box and cooled by an electric fan.

On the morning of treatment no breakfast was given (unless noted otherwise). The patient was weighed, then he lay on the hypertherm bed for at least twenty minutes, following which pulse rate and blood pressure readings were obtained every three to five minutes for at least fifteen minutes. A velocity rate was then determined and in ten patients repeated. Fever treatment was then started, and body temperature was raised as rapidly as possible to the desired height, usually in about one and one-half hours. The hypertherm current was then turned off, and the patient wrapped in blankets to maintain the body temperature at levels of 104° to 106° F. (R) for three to five hours. Three to six velocity determinations were made during the fastigium of fever. Immediately preceding these determinations, pulse rate, blood pressure, and temperature readings were obtained. Fluids consisting of 0.6 per cent saline were given freely during the treatment, with the result that patients as a rule showed only a slight loss (0-2½ pounds) in weight and in some instances an increase (0-2 pounds) occurred. One patient (A. A.) showed a loss of 6 pounds as a result of treatment.

RESULTS AND DISCUSSION

Seventeen hypertherm treatments were given to fifteen patients during which velocity rates were determined before and during induced fever. In twelve patients the initial velocity rates (Table I) were normal,[5] varying from 14 to 20½ seconds. In the remaining three patients (G. O., J. N., and D. T.) the velocity rates were slower than normal, 23, 26, and 35 to 41 seconds, respectively. The slow velocity time of patient G. O. is due, not to the presence of a rheumatic valvular lesion, but to early symptoms of myocardial insufficiency, palpitation and dyspnea of which he complained. Patient J. N. revealed no cardiac

pathology on examination, but because of a tabetic gastric crisis frequent vomiting occurred, with a resultant dehydration and an increase in the viscosity of the blood. This is probably responsible for the slow velocity time since the flow of a fluid in a tube is inversely proportional to the viscosity of the fluid (provided other factors remain equal), and it has already been shown[1] that in polycythemia the increase in blood viscosity is accompanied by a slowing of the circulation time. The rather marked slowing of the velocity of flow in patient D. T. is due to an impaired myocardium as seen from the findings of a hypotension, 87/64 mm. Hg, and feeble heart sounds.

TABLE I

VELOCITY RATES BEFORE FEVER INDUCTION

PATIENT	VELOCITY TIME (IN SECONDS)	PATIENT	VELOCITY TIME (IN SECONDS)
A. A.*	15 14	A. M.	17½ 19
R. St.*	16 15 14	S. M.	18½
R. S.	17 15	L. G.	19
J. P.	15 16½ 17½	J. M.	19½ 20½
F. K.	15⅓ 20⅓ 18	G. O.	23
B. C.*	15½ 20½	J. N.	26
J. Mg.	16 16½	D. T.	41 35
G. M.	17		

*Breakfast before treatment.

Duplicate initial velocity rates were obtained on ten patients and showed normal variations of 2 seconds or less in seven.[5] In the remaining three patients (F. K., B. C., and D. T.) variations of 5, 5 and 6 seconds, respectively, occurred. The greater than normal variations occurring in patients F. K. and B. C. are probably due to the apprehension of both patients before fever induction; that of patient D. T. can be attributed to the very slow velocity time, the variations becoming greater as the slowing of the circulation time increases.

When the initial velocity rates of the group are taken as a whole, no relationship can be found between the velocity of flow and other clinical findings such as pulse rate, body temperature, systolic, diastolic, and pulse pressures.

TABLE II

VELOCITY RATES DURING PROLONGED HYPERPYREXIA

PATIENT	AGE	DIAGNOSIS	TIME	B. P.	PULSE	TEMP. (F.)	VELOCITY (SEC.)	COMMENT
G. O.	47	General paresis	9:22	132/87	92	99.2	23	Rheumatic heart disease: mitral stenosis
			1:15	100/60	132	105.8	13½	
			2:45	100/64	134	105.0	14	
			3:22	98/56	144	105.6	13	
A. M.	44	General paresis	9:12	116/77	77	98.6	17½	
			9:18				19	
			11:32	136/ 0	129	105.6	10¼	
			12:17	128/ 0	129	105.6	10⅓	
			2:02	130/ 0	134	105.0	11	
			2:42	130/ 0	144	106.0	10½	
R. St.	29	Multiple sclerosis	10:05	113/90	74	98.4	16	Breakfast at 6:30 A.M.
			10:15				15	
			12:20	132/50	134	104.8	9	
			1:15	103/28	122	104.4	8½	
			2:00	124/40	140	105.0	9½	
			2:22	125/70	134	105.0	8⅔	
			9:03	123/89	72	99.2	14	
			11:20	140/50	124	105.0	9⅔	
			12:33	146/46	135	104.5	8¼	
			1:32	120/60	144	104.0	10	
			2:28	122/40	144	103.6	8	
			3:29	100/25	147	104.8	11	
J. P.	40	Gonorrheal urethritis	9:01	103/69	64	97.6	15	
			9:12				16½	
			11:30	122/ 0	148	106.4	12	
			12:28	76/ 0	141	105.8	12	
			1:32	82/30	152	105.0	12	
			2:28	88/ 0	145	106.0	11	
			8:30	98/66	58	98.4	17½	
			12:50	96/40	135	104.0	13½	
			1:38	104/ 0	144	105.0	10½	
			2:08	108/10	148	105.6	12½	
			2:54	98/ 0	147	106.0	13	
			3:31	86/ 0	144	106.0	12	
G. M.	23	Congenital syphilis Interstitial keratitis	9:20	117/49	71	99.0	17	
			12:32	150/ 0	112	105.0	9½	
			1:20	146/ 0	110	104.0	9½	
			1:55	140/ 0	117	103.6	10	
			2:50	138/ 0	110	103.4	10½	
R. S.	24	Wassermann-fast syphilis	10:56	130/76	87	98.0	17	
			11:00				15	
			1:40	110/60	125	104.8	16	
			1:45	110/60	125	104.8	14½	
			3:43	102/60	117	104.0	14	
F. K.	48	General paresis	9:11	115/75	85	99.0	15½	
			9:16	115/75	85	99.0	20⅓	
			9:22	115/75	85	99.0	18	
			11:18	142/60	144	105.6	10½	
			11:44	114/ 0	162	106.4	13	
			1:50	108/ 0	140	106.0	10½	
			2:11	104/ 0	165	106.2	11½	

TABLE II—CONT'D

PATIENT	AGE	DIAGNOSIS	TIME	B. P.	PULSE	TEMP. (F.)	VELOCITY (SEC.)	COMMENT
J. Mg.	27	Gonorrheal urethritis and arthritis	9:22	130/65	90	100.2	16	
			9:34				16½	
			11:12	125/ 0	140	105.0	8	
			12:01	124/ 0	129	105.0	9½	
			12:55	125/ 0	123	104.4	6½	
			1:15	125/ 0	124	104.0	10½	
J. M.	28	General paresis	9:40	97/54	73	99.0	19½	
			9:45				20½	
			11:55	130/ 0	156	105.2	7½	
			12:23	110/ 0	156	106.2	7½	
			1:23	114/ 0	146	105.6	10½	
			2:32	102/ 0	132	105.0	11	
			3:15	106/ 0	134	104.0	11½	
			3:20	106/ 0	134	104.0	8	
J. N.	37	Tabes dorsalis with gastric crisis	9:48	123/86	88	98.6	26	
			12:30	120/60	140	106.0	11½	
			1:15	120/56	140	105.8	11	
			2:30	90/40	128	105.0	16	
S. M.	36	General paresis	9:30	103/69	81	99.2	18½	
			11:37	100/58	120	106.2	8½	
			12:30	102/20	132	106.0	9	
			1:32	102/60	120	105.2	14	
			2:30	108/66	100	104.0	12	
D. T.	46	General paresis hypotension	9:45	87/64	52	98.6	41	Heart sounds of poor quality. Paraldehyde 8 c.c. at 10:00 A.M.
			9:55				35	
			11:55	128/76	122	106.0	13	
			1:25	110/74	120	106.2	14	
			1:57	106/70	124	105.8	11⅔	
			2:50	90/62	112	105.0	17½	
B. C.	21	Congenital syphilis Interstitial keratitis	10:05	125/77	87	100.0	15½	Patient had breakfast at 6:30 A.M.
			10:10				20½	
			12:16	132/ 0	112	105.6	9½	
			1:03	120/10	104	105.6	12⅔	
			1:50	112/30	108	104.8	11	
			2:48	106/ 0	114	104.4	15½	
L. G.	47	Primary optic atrophy	9:50	128/78	88	98.8	19	
			11:30	134/54	148	105.0	15⅓	
			12:18	115/60	138	105.0	18½	
			1:03	86/50	140	105.0	11½	
			1:37	90/50	140	104.8	14½	
A. A.	53	Primary optic atrophy	9:45	133/68	83	99.0	15	Cerebral thrombosis during treatment Breakfast at 6:30 A.M.
			9:50				14	
			11:43	120/ 0	148	106.0	8	
			12:28	106/ 0	162	107.2	12½	
			12:58	84/ 0	168	107.0	13½	
			1:50	78/44	132	105.8	14	
			2:32	84/ 0	120	106.0	15	
			3:13	110/44	120	106.0	7	

VELOCITY RATES DURING FEVER

Seventy-one velocity rates obtained during the prolongation of high body temperature during seventeen fever treatments showed, with but four exceptions, a hastening in the velocity of flow over that obtained

before the induction of fever (Table II). The four exceptions (one each in patients R. S. and B. C., two in patient A. A.) revealed velocity rates at a temperature of 104.4° to 106° F. which were equal to that obtained before the induction of fever. At no time was the circulation time during fever slower than that obtained at normal body temperature. The hastening of the circulation was accompanied by a more rapid pulse rate and in most cases by an increase in the pulse pressure, brought about as a rule, by a rise in the systolic and a marked fall in the diastolic level. The greatest shortening of the circulation time during sustained fever occurred in patient D. T., from 117 per cent to 225 per cent for a temperature of 105 to 106.2° F., accompanied by an increase of from 115 per cent to 138 per cent in the pulse rate. Patient J. P., who showed a nearly similar increase in the pulse rate (from 120 per cent to 155 per cent for a sustained temperature of 104 to 106.4° F.), revealed increases of only from 30 per cent to 67 per cent in the velocity time. The small-

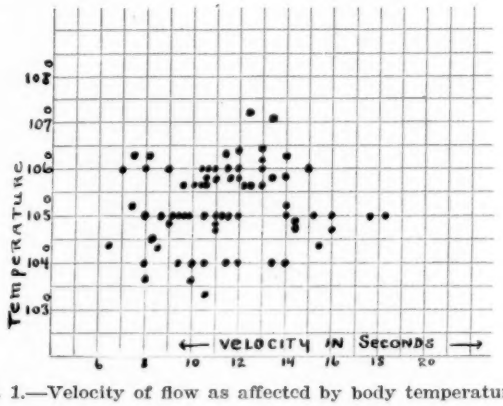

Fig. 1.—Velocity of flow as affected by body temperature.

est increase in the velocity time occurred in patient R. S.—from 0 to 13 per cent for a body temperature of 104 to 104.8° F. No definite relationship could be found in the individual patient between the velocity of flow during sustained fever and other clinical findings (body temperature, pulse rate, systolic, diastolic, and pulse pressures). When the results of the group are taken as a whole, variations in the velocity time as great as 11 seconds occurred for nearly similar body temperatures (Fig. 1). A suggestive linear relationship is seen best between the velocity time and the systolic blood pressure, less so between the velocity time and the pulse pressure (Fig. 2).

The results obtained during sustained fever can be divided roughly into two groups:

Group 1. Seven patients (G. O., A. M., R. St., J. P., G. M., R. S., F. K.) who showed a fairly constant velocity rate, individual variations of 3 seconds or less for body temperature fluctuations from 0.6 to 2° F. during nine fever treatments.

Group 2. The remaining eight patients (J. Mg., J. M., J. N., S. M., D. T., B. C., L. G., A. A.) who showed individual variations of from 4 to 8 seconds for body temperature fluctuations of 0.2 to 2.2° F. during eight fever treatments.

The differences between these two groups cannot be attributed to the more marked changes in other clinical findings (i.e., pulse rate, body

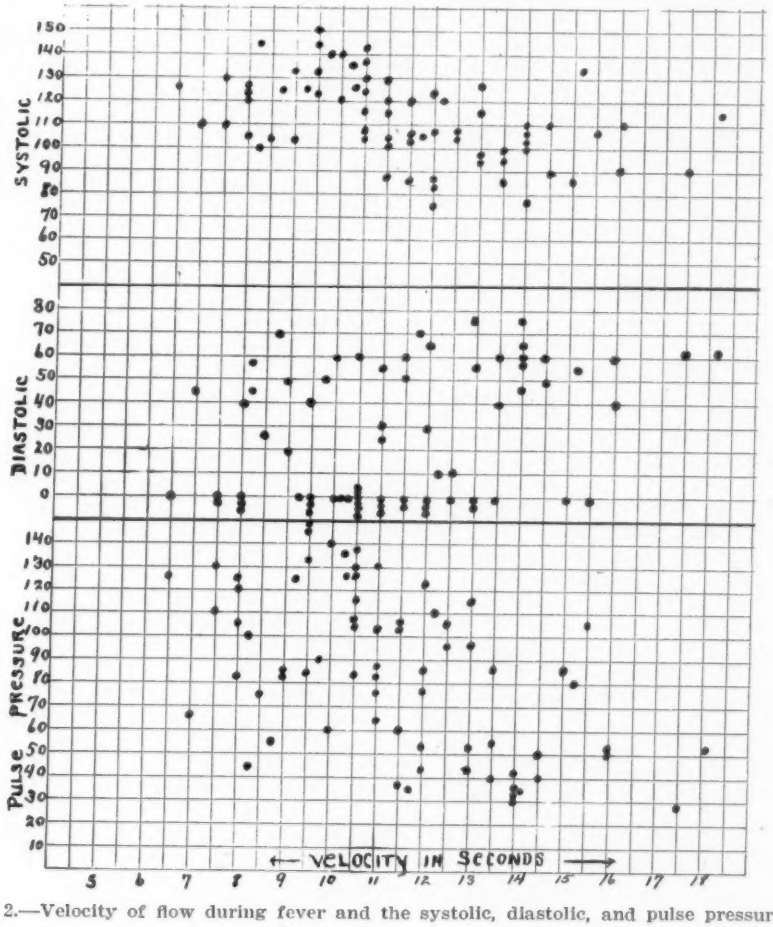

Fig. 2.—Velocity of flow during fever and the systolic, diastolic, and pulse pressures.

temperature, systolic, diastolic and pulse pressures) in one than in the other. It cannot be explained by the degree of restlessness or discomfort during fever, as seen from the results obtained in patients R. S. and B. C. Both patients exhibited a marked degree of restlessness and discomfort and yet the velocity rates in the former were fairly constant and in the latter revealed fluctuations as great as 6 seconds, the pulse rate, blood pressure and body temperature changes being slight and not accounting for the differences obtained.

With an increase in body temperature, such as occurs in artificial fever, body metabolism is increased[7] and the blood flow to the tissues, with their greatly increased vascular bed, is hastened. The pulse rate and the pulse pressure, signifying as a rule a greater cardiac output, are increased. The venous pressure must increase in order to permit a greater return to the heart. Were all these changes, together with the blood volume, constant for a specific temperature, one would expect a fixed increase in the circulation time.

At fairly constant sustained temperature levels during artificial fever the increase in the metabolic rate is not fixed;[7] the venous pressure shows fluctuations in both directions;[8] the area of the vascular bed is not constant;[9] and the plasma volume shows variable degrees of concentration.[8] In addition, the pulse rate and the pulse pressures vary. Since all these factors show inconstant changes, the circulation time should do likewise, greater fluctuations in the velocity time occurring in those patients in whom these changes are more marked.

In patient A. A. no hastening of flow occurred on two occasions at temperatures of 105.8 and 106° F. This was accompanied by a marked drop in blood pressure from a level of 133/68 before treatment to 78/44 and 84/0, a forerunner of peripheral vascular shock brought on by exposure to hot moist air.[8] The failure of the velocity of flow to be hastened at these high temperature levels, the marked drop in blood pressure, the reduction of the blood plasma volume which occurs[8] (especially so in this patient in view of the loss of 6 pounds in body weight during treatment), all were of importance in the development in this patient of a cerebral thrombosis during treatment. With a subsequent rise in the systolic blood pressure a hastening of the blood flow occurred.

The velocity rates obtained during sustained fever reveal that no other clinical finding is indicative of the rapidity of the blood flow under these conditions. The pulse rate and blood pressure, which to some denote the state of the circulation, do not indicate the degree of fluctuation in the circulation time which may occur. This again emphasizes the importance of the velocity of blood flow as an index of cardiac effort under conditions of stress.

SUMMARY

Therapeutic fever was induced on seventeen occasions in fifteen male subjects by means of the Kettering hypertherm and the arm-to-carotid circulation time determined before and during the prolongation of high body temperature.

In twelve patients the initial velocity rates before fever induction were normal, ranging from 14 to 20½ seconds. In three patients the initial rates were below normal, 23 to 41 seconds, and are attributed in two patients to myocardial degeneration and in the third to increased viscosity of the blood as a result of repeated vomiting.

Seventy-one determinations of the circulation time at temperature levels of from 103.4 to 107.2° F. prolonged from three to five hours revealed a hastening of the velocity of the blood flow on all but four occasions. In the individual patient no definite relationship was found between the velocity of flow during sustained fever and the body temperature, pulse rate, systolic, diastolic or pulse pressures.

In seven patients the shortened circulation time during sustained fever was fairly constant, revealing fluctuations of 3 seconds or less for body temperature changes of 0.6 to 2° F. In the remaining eight patients variations of 4 to 8 seconds occurred for body temperature changes of 0.2 to 2.2° F.

The greater fluctuations in the circulation time in the second group are attributed to greater variations in concomitant phenomena during fever, among them the metabolic rate, venous pressure, plasma volume, and area of the vascular bed.

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LIGATION OF THE CORONARY ARTERIES IN JAVANESE MONKEYS*†

I. Introduction, General Experimental Results, Especially the Changes in the Ventricular Electrocardiogram

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THE problem of what changes take place in the electrocardiogram owing to local disturbances of the coronary circulation is of great interest both physiologically and clinically. The physiologist hopes to be able to extend his knowledge of the construction of a normal electrocardiogram by comparative studies of these changes, looking in his experiments for a relationship between definite changes in the electrical curves and functional disturbances in definite parts of the heart. As has been mentioned by Lewis,[1] "the cutting out of large areas of the musculature by obstructing the blood supply should ultimately prove of value in arriving at conclusions as to the manner in which the normal electrocardiogram is produced." The clinician hopes that electrocardiographic changes will be of value in diagnosis, and in studying the course of diseases and the results of his treatment in patients with disturbances of the coronary circulation and heart muscle function.

Although extensive work has been carried out on this subject both experimentally and clinically and is still being carried out daily (see for general information, among others, Condorelli,[2] Hochrein,[3] Lian[4] and Hyman and Parsonnet[5]), we were of the opinion that an experimental investigation in monkeys might contribute to our knowledge; the more so since, as far as we know, it had never yet been made.

This article describes the results of experiments which we have been conducting since 1933 on the Javanese monkey, *Macaca irus* (nomenclature of Hartman and Straus,[6] formerly called Cynomolgus).

For experimental electrocardiographic researches, especially when it is desired to apply the results of the experiments to human physiology and clinical medicine, monkeys take the first place among all experimental animals. As has been shown in previous papers[7] and is reproduced in Fig. 1, the monkey heart has great similarities both anatomically and physiologically with the human heart, especially as far as the internal structure, the position in the thorax, and the fixation through adhesions of the pericardium to the diaphragm are concerned. These factors are of great importance in determining the form of the electrocardiogram, which we have found in practice to show a far

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†Preliminary communication on portions of the subject matter of this paper was made to the Seventh Science Congress at Batavia, Java, on October 25, 1935.

more constant configuration in Macaca than, for instance, in dogs. Changes in the form of the electrocardiogram are not so easily caused in monkeys as in other animals by changes in position of the heart and may, therefore, with far greater certainty be attributed to changes in the function of that organ. In our opinion, then, it is quite correct that warnings should be appearing in ever increasing number against applying to man results and data obtained by experiments on dogs.[8, 9, 10]

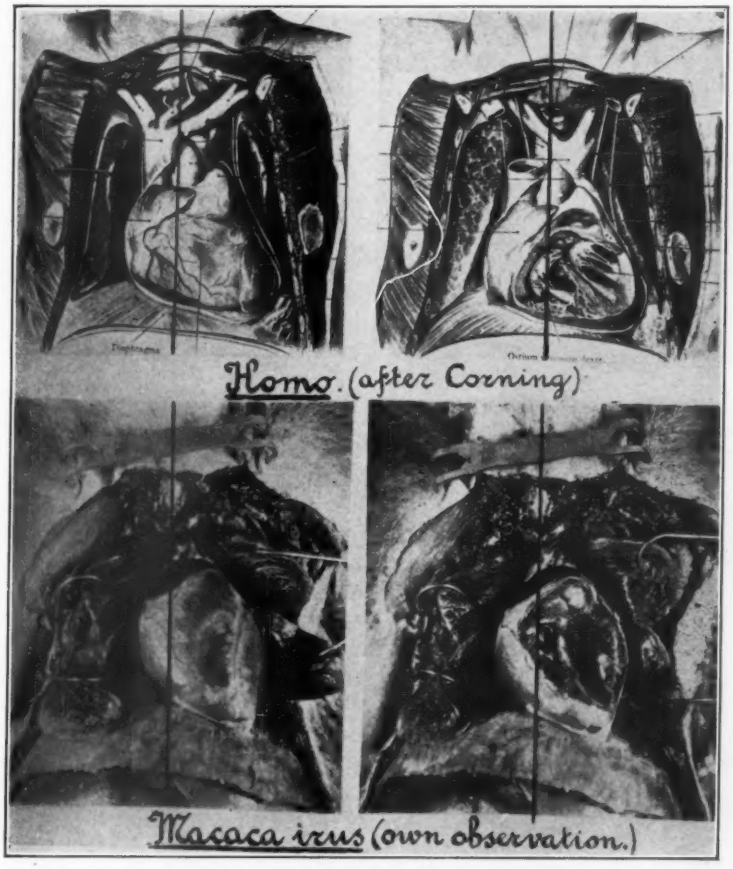

Fig. 1.—See text.

We were disappointed in our expectation that the monkey, or at any rate *Macaca irus,* in addition to structure, position, and fixation of the heart, would also show great similarity to man in the anatomical relationships of the coronary arteries. We found that in the great majority of these monkeys the ramus descendens posterior was a branch of the left coronary artery, a condition found in only from 10 to 20 per cent of hearts in man.[2*]

*In the anthropoid apes, among others the Hylobates, we thus far have found the ramus descendens posterior without exception branching from the right coronary artery. These animals approximate man most closely, and in all probability also in the structure of their coronary system.

When in fresh *Macaca irus* hearts the orifices of the coronary arteries in the sinus of Valsalva are observed, the left artery usually gives the impression of being larger in diameter than the right, whereas in man the opposite is usually the case.[11] With the aid of sounds of known diameter an approximate measurement was made of the diameter of the orifices of the coronary arteries in nineteen fresh Macaca hearts. In fifteen of these hearts the left artery was definitely larger in diameter than the right, while in the other four the diameters of the right and left artery were the same. The average diameter of the left arteries was 1.60 mm., that of the right arteries was 1.26 mm.

In direct agreement with this result we found by experiments with isolated *Macaca irus* hearts, prepared according to the method of Langendorff, that ligation of the left artery reduced the coronary flow more than ligation of the right artery. The areas supplied by the arteries were determined in another twenty of these monkeys by in-

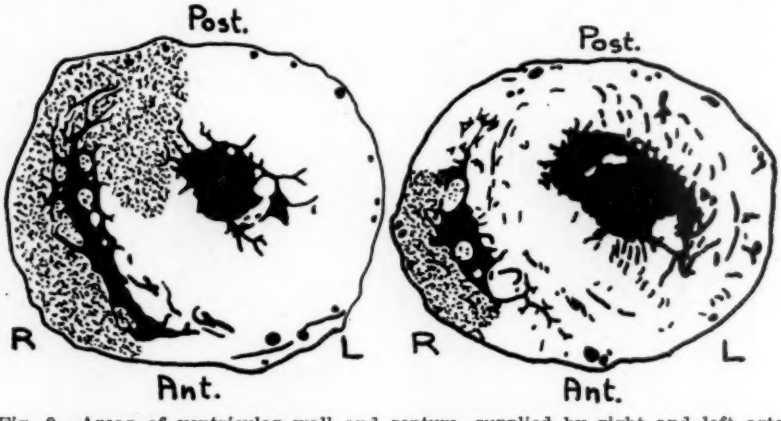

Fig. 2.—Areas of ventricular wall and septum, supplied by right and left artery, respectively, in Macaca. The degree of preponderance of the left artery differs in various specimens. Two types are shown. Both hearts were cut through the middle, perpendicularly to the axis.

jection of carmine gelatin and Berlin blue gelatin through the orifices, after the method of Romeis.[12] The result we usually obtained is shown in Fig. 2.

In *Macaca irus* the following distribution is seen: *Left coronary artery:* left auricle and auricular appendix; the whole wall of the left ventricle, anterior and posterior; sometimes the whole septum, sometimes only the anterior two-thirds of the septum; often the lower apical portion of the anterior surface of the right ventricle and a strip of the right ventricle along the sulcus longitudinalis anterior; all the papillary muscles and the trabeculae on the left side and the anterior papillary muscles and trabeculae on the right side. *Right coronary artery:* right auricle and auricular appendix; the interauricular septum; the region around the sinus node; the whole lateral and posterior wall of the right ventricle; often the posterior one-third of the interventricular septum; the anterior wall of the right ventricle with the exception of a strip along the sulcus longitudinalis anterior; and the posterior papillary muscles and trabeculae on the right. Individual variations were observed, especially where the blood supply of the septum was concerned.

In the relationships of the coronary arteries, therefore, *Macaca irus* shows a certain resemblance to the dog.[2] We merely call attention to this fact, but the relations mentioned do not, in our opinion, offer any objection to using these monkeys for seeking a possible connection between changes in the electrocardiogram and a possible area of disturbed function eventually to be localized macro- and microscopically since we may expect that as far as the electrocardiogram is concerned, the localization of the lesion is determinative, independently of whether the lesion was caused by a disturbance of the left or right artery.[13] For example, it would make no difference to the electrocardiographic results of a bundle-branch section whether that section were made with the right or with the left hand! For electrocardiographic studies the Macaca heart, because of its more human architecture, position and fixation, and, as was recently pointed out, also the more human form of the Macaca thorax,[14] will maintain its advantages for physiology and clinical medicine even though the coronary distribution is somewhat different from that in man.

Coronary ligations have been attempted but seldom in monkeys. Hirsch[15] ligated the ramus descendens anterior of the left coronary artery in two monkeys (species not mentioned) and observed no permanent change in the heart action; there appeared a temporary arrhythmia. No records were made; the experiment was principally carried out to obtain further insight into the question whether the coronary arteries anatomically or functionally must be regarded as end-arteries. Spalteholz found in these monkeys *myomalacische Schwielen,* but his illustrations[15] refer only to dog hearts.

We have found in the literature only two additional reports of experimental research on the coronary arteries in monkeys. Sutton and Lueth[16] in their attempts to produce experimentally pain by operative interference on the heart and vessels of dogs used "as a check" one monkey (Macaca?). They opened its thorax under local anesthesia and clamped off one of the coronary branches. According to their report, the dimensions of the heart were too small for them to be able to carry out their original plan and ligate the artery. Barbour and Prince[17] studied the effect of epinephrine on the coronary circulation of isolated hearts of the *Macaca rhesus.*

In none of these publications was any mention made of electrocardiographic investigations.

We shall now discuss our experiments and the results we obtained in monkeys of the *Macaca irus* variety, one of the common Java monkeys, weighing between 3 and 7 kilograms.

In these experiments we limited ourselves to the ligation of the *ramus descendens anterior of the left coronary artery,* about 2 to 3 mm. distal to the origin of the ramus circumflexus, and the ligation of the

principal stem of the right coronary artery, about 5 mm. distal to its origin from the aorta, in the auriculoventricular groove below the right auricular appendix.

These customary ligation sites are shown in the accompanying diagram (Fig. 3).

Technic.—For the details of the technic used by us in making electrocardiograms of monkeys either in three leads simultaneously or successively, and also for certain physiological peculiarities of monkey hearts,* we refer to former publications.[7] Particular attention was paid to avoiding technical errors, since, especially in the monkey heart with its rapid action, they might readily lead to distorted records.

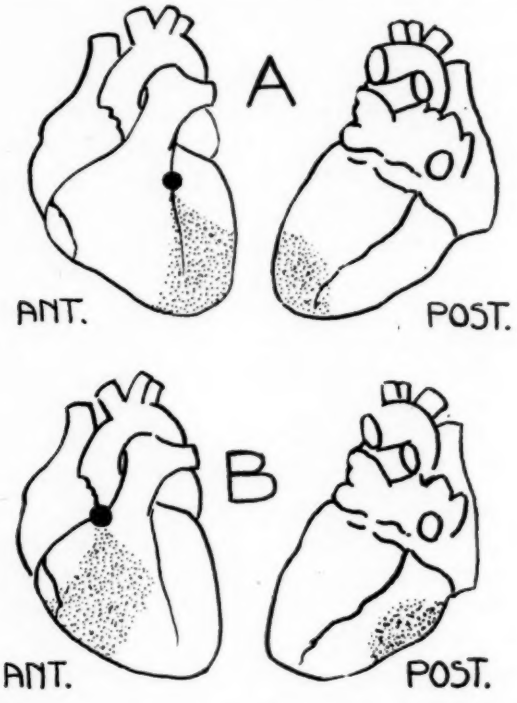

Fig. 3.—Usual site of ligation of the ramus descendens anterior and of right artery, and areas which showed obstructed circulation in injected preparations.

We assured ourselves that we could rely entirely on our curves, made as they were with high registration speed by the latest model of Cambridge galvanometers at a projection distance of 120 cm. In our experience the so-called "modern" electrocardiographs are often unable to record accurate curves at heart frequencies such as occur in monkeys. We used, before passing on to coronary ligation in the remaining monkeys, fifteen monkeys solely and especially to investigate the effects on the electrocardiogram of various factors such as narcosis, opening the trachea, artificial respiration, opening the thorax, pneumothorax, opening the pericardium, exposing the heart, wounding the heart without coronary ligation, changes in body position, asphyxia, and so forth. Many observers[9, 18, 19, 20] have quite correctly called atten-

*The pulse rate average in these monkeys is 225 per minute; the P-R interval about 0.07 sec.; the QRS complex about 0.03 sec.; systole lasts somewhat longer than diastole.

tion to the fact that such factors might well lead to distortions in the electrocardiogram. It is our experience, however, that they may be left out of consideration as causes of distortion if the following operative technic be used in the ligation:

After the animal has been placed on its back and connected to the electrodes in the manner earlier described[7] and after the skin of the thorax has been shaved and sterilized by the application of tincture of iodine, as a narcotic, pernocton, 0.3 c.c. of a 10 per cent solution, or evipan sodium, 0.2 c.c. of a 10 per cent solution per kilogram of animal weight is injected intravenously very slowly. Then the trachea is opened and connected to a Palmer respiration apparatus driven by direct current; the skin and subcutaneous tissues are then cut through, on the left for access to the left coronary artery, on the right for the right coronary, and in both cases close to the sternum. The ribs from the second to the fifth are then cut through close to the sternum, care being taken to avoid the internal mammary artery, which should be ligated if it is accidentally cut. The thorax is then pressed open with a self-retaining wound retractor and the lung protected by gauze soaked in physiological saline. The pericardium is next opened and the flaps are turned back and fixed by hemostatic forceps so that the heart is left quietly beating in the pericardial bed. A ligature of silk or catgut is then passed around the artery desired by means of a very fine curved needle and the vessel is then tied off. The pericardium is sutured by catgut. The thoracic wound is then closed layer by layer while, the animal being disconnected from the respiration apparatus, the operator by carefully blowing up the lungs can be sure that no pneumothorax will follow. The skin wound is closed by metallic skin clips and gauze painted with a mastic solution. The tracheal cannula is then removed and the tracheal wound closed. We have found that if no ventricular fibrillation develops the animals breathe spontaneously at once and awaken from the narcosis in from one-half to one hour and that they are at once lively, take food, and as a rule show no signs of suffering any pain.

We shall consider exclusively results from successful experimental ligations, by which we mean: 1. Completely satisfactory course of both narcosis and operation with no significant postoperative rise or fall of body temperature, no significant hemorrhage, no pneumothorax, and no infection; 2. An actual closing off of the artery desired, controlled post mortem both macroscopically and microscopically.

In these small hearts beating with high frequency it is often practically impossible to ligate the arterial branch desired without including in the ligature one or more of the accompanying veins, which often lie superficial to the artery. This happened several times, but, according to others,[9, 10, 21] it does not affect the results of ligation experiments in any material way. The microscopic examination showed that quite often small nerve fibers were also included in the ligature. We attach practically no significance to these accidental ligations since the obstruction of the coronary arteries from within by lycopodium, by which the nerves are spared, gives results similar to closing them off from without, at least in dogs[19]; damage to the outer side of the vessels in Macaca left no definite electrocardiographic changes after the circulation had been restored (see the clamping experiment described in Part III of this paper), and air embolism is capable of producing comparable changes (Fig. 17). We believe, however, that it is possible that these nerve ligations may be responsible for the fact that our monkeys, as a rule, showed no signs of pain. In this we agree with Sutton and Lueth.[16]

If we designate our animals by the numbers they bear in the collections of laboratory specimens, and further mark those monkeys in which the ligation of the ramus descendens anterior was applied with

TABLE I

SEE TEXT

MONKEY	DATE OF OPERATION	S-T DEVIATION AFTER OPERATION			SURVIVAL AFTER OPERATION	CAUSE OF DEATH*	REMARKS
		FIRST REG.	MAXIMUM	DISAPPEARED			
4 L	3/21/33	5 min.(A)	± 2 hr.	± 1 wk.	6 mo.	Killed	First S-T deviation Type A, after ±5 months other Type B. See text.
		± 5 mo.(B)	± 6 mo.	?			
5 L	3/22/33	20 min.	?	?	36 min.	Fibrillation	
9 L	4/12/33	3 min.	± 2 hr.	± 5 mo.	5½ mo.	Killed	
13 L	5/13/33	?	?	?	23 min.	Fibrillation	Fibrillation occurred before thorax was closed.
15 L	6/20/33	8 min.	>29 min.	?	33 min	Fibrillation	Deviation still increasing when fibrillation occurred.
16 L	6/21/33	2 min.	?	?	13 min.	Fibrillation	Bundle-branch block. See text.
17 L	10/18/33	± 4 min.	51 min.	± 1 day	2 days	?	Probable cardiac failure.
19 L	10/24/33	± 2 min.	64 min.	± 2 wk.	2 mo.	Fibrillation	Small amount of chloroform. See text.
26 L	11/28/33	?	?	?	27 min.	Fibrillation	Fibrillation at first registration after operation.
35 L	3/ 9/34	13 min.	56 min.	± 6 hr.	2 mo.	Killed	
44 L	3/20/34	9 min.	±1½ hr.	±1½ mo.	1½ mo.	Killed	Small deviation still present at death.
49 L	4/18/34	22 min.	68 min.	± 5 days	5 days	Fibrillation	Small deviation just before fibrillation.
51 L	5/ 9/34	±20 min.	28 min.	± 1 mo.	±1 mo.	Killed	Small deviation still present at death.
52 L	5/ 1/34	13 min.	>16 min.	?	16 min.	Fibrillation	Deviation still increasing when fibrillation occurred.
53 L	5/25/34	18 min.	± 6 days	± 1 mo.	1 mo.	Killed	Small deviation still present at death.
AG L	4/ 5/35	± 8 min.	?	?	±1 hr.	Killed	Temporarily closed, metal clip. See text.
{6 L	3/28/33	1 min.	±55 min.	± 7 wk.	7 wk.	?	{Died 7 weeks after L., some hours after secondary
}6 L+R	5/17/33	±20 min.	±64 min.	?	? hr.	?	} ligation of R. Probably no fibrillation. See text.
10 R	4/20/33	2 min.	58 min.	± 5 mo.	6 mo.	Killed	
11 R	4/21/33	15 min.	±40 min.	± 1 day	6 mo.	Killed	
12 R	5/ 3/33	3 min.	±63 min.	± 1 day	5½ mo.	Killed	
14 R	6/14/33	–	–	–	4 mo.	Killed	No S-T deviation. See text.
23 R	11/12/33	2 min.	±49 min.	?	6 hr.	?	Heart failure? Fibrillation not impossible.
25 R	11/24/33	4 min.	> 9 min.	?	1 hr.	?	No fibrillation. See text.
31 R	1/13/34	–	–	–	1 mo.	Killed	No distinct S-T deviation. See text.
36 R	3/ 2/34	22 min.	± 1 hr.	?	6 hr.	?	Probable fibrillation.
37 R	3/ 6/34	15 min.	±43 min.	?	1 hr.	?	No fibrillation. See text.
40 R	3/26/34	10 min.	?	?	35 min.	Fibrillation	
41 R	3/13/34	7 min.	±57 min.	± 1 day	4 days	?	Fibrillation not excluded. See text.
43 R	3/20/34	15 min.	75 min.	±12 days	1½ mo.	Killed	
56 R	5/15/34	20 min.	± 2 hr.	± wk.	3 wk.	Killed	
X R	3/11/34	± 5 min.	?	?	25 min.	Fibrillation	Vagi cut. See text.

*Killing was done by rapid intravenous injection of 6 to 8 c.c. of pernocton or evipan sodium.

an "L" and those in which the right artery was ligated with an "R," we obtain the following summary of our experimental material (Table I).

In total, therefore, we include in this report thirty-one monkeys. In seventeen of these animals the left ligation was applied and in fourteen the right. In one monkey (No. 6) first the left ligation was employed, and after seven weeks at a second operation the right ligation was made.

Electrocardiograms of each monkey (with the animal always in the same body position, horizontal and lying on its back) were made before the narcosis, during the narcosis, during various phases of the operation, and at various times after the operation. Records were made of the three classical leads, sometimes successively, but usually simultaneously.* We soon stopped making records during the operations while the thorax was still open as there were too many possible sources of error introduced.[1, 10, 22, 23]

We observed various changes, especially in the ventricular electrocardiogram, and, further, arrhythmias, either accompanied by disturbances of conduction or not, such as extrasystoles, paroxysmal tachycardia, ventricular fibrillation, auriculoventricular block, delayed intraventricular conduction, bundle-branch block and nodal rhythm, all of which will be discussed below.

CHANGES IN THE VENTRICULAR ELECTROCARDIOGRAM

These can be divided into early (primary) changes and late (secondary) changes.

Among the former a definite displacement of the S-T segment, which in normal monkeys is isoelectric, was the most striking. This S-T deviation was found in all but two of the "left monkeys" (13 L and 26 L) and all but two of the "right monkeys" (14 R and 31 R). This was easily explained in the case of the two left monkeys since even by the time of the first recording after closing the thorax they both showed ventricular fibrillation. In the case of the two right monkeys it is probably connected with the peculiar position and size of the heart lesion which will be further discussed later.

We did not observe a similar rapid displacement of the S-T segment even in severe operations, unless a coronary artery was ligated. It was not caused by the thorax operation as such. This fact is illustrated by Fig. 4.

Calculated from the moment of ligation, the time at which the S-T deviation was first observed, at which it reached its maximum, and at which it disappeared (as far as the subsequent duration of life of

*In the curves reproduced, the three leads which were taken successively are separated by black horizontal lines; those not marked in this way are all simultaneous recordings. Sometimes, to save room for reproduction, the blank spaces between curves were partly cut away, identical phases again being placed in their original time relation to each other. Reprints of the original curves will be sent on request. The time is, as a rule, marked in ½ and ⅕₀ sec., sometimes also in ⅒ sec.; 10 scale divisions represent 1 millivolt.

the animal allowed us to observe this latter point) will be found in Table I. It will be seen that, except in the special Case B of Monkey 4 L, the beginning of the deviation was registered on an average of about ten minutes after the ligation; however, it was often registered sooner, sometimes after only one or two minutes. In general the condition developed so rapidly that, practically speaking, a trained eye could see the typical changes in movement of the string even before the thorax was closed, and thus we knew that the ligation had been a success. Since we usually waited to make our first record after the operation until the thorax had at least been provisionally closed, the actual moment at which this phenomenon began, certainly should have fallen below the above mentioned average. This is in accordance with the observations of Wood and Wolferth[10] in dogs.

In as far as it was possible to determine, the maximum S-T deviation was reached in an average of sixty-three minutes (excluding cases

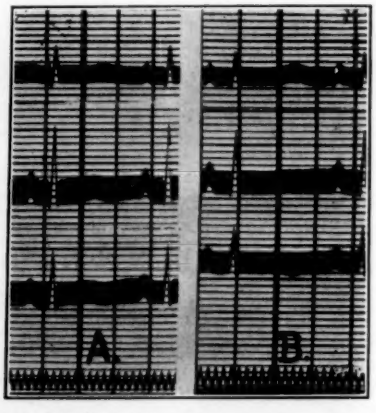

Fig. 4.—Control animal, Monkey 34, Leads I, II, and III. *A*, before operation; *B*, 2 hours after complete operation for ligation of the ramus descendens anterior, in which the ligature, as was found microscopically, missed the artery and included only fat. No change in electrical curve. No S-T displacement. Time marked in $\frac{1}{10}$ and $\frac{1}{50}$ sec.

4 L (B), and 53 L); it was practically never seen under twenty-eight minutes after the operation. The time within which the S-T segment again became isoelectric varied greatly. In our observations the minimum time was six hours and the maximum about five months after the operation, with an average of about one month. This time relationship must be considered of importance for a possible explanation of the deviation, which will be discussed in Part III of this paper.

A preliminary, but incomplete, impression of the deviations which occurred in our experiments may be obtained by observing only the upward or downward displacements without regarding the magnitudes of these displacements. If an S-T movement upward is indicated with ↑ and one downward with ↓ and an isoelectric state of the S-T segment with =, Table II will show the S-T displacements we observed in our monkeys.

At first glance it seems that greater regularity occurs in the cases of right ligation. The S-T deviation in the right monkeys was never upward in Lead I, but in almost all cases downward, while in Lead III the deviation was almost always upward. The deviation in Lead II was about equally often concordant with that in Lead I as with that in Lead III so that Lead II, contrary to reports of other investigators,[13] in itself cannot be a guide for the type of curve.

There is seemingly less regularity in the results of the left ligation although S-T is more often deviated upward than downward in Lead I and the opposite holds good for Lead III. S-T in Lead II, as a rule, took the same direction as in Lead III even when in Lead I it was diverted upward and in Lead III downward.

TABLE II

DISPLACEMENTS OF S-T SEGMENT AS FOUND IN THE THREE LEADS
(SEE ALSO TEXT)

LEFT (ram. desc. anterior).

	4a	4b	5	6	9	15	16	17	19	35	44	49	51	52	53	AG
I	↓	↑	↑	↓	↑	=	↓	↑	↓	=	↑	↑	=	↓	↑	↑
II	↓	↑	↓	↑	↑	↑	↑	↓	↑	↓	↓	↓	↑	↓	↓	↑
III	↓	↓	↓	↑	↑	↑	↑	↓	↑	↓	↓	↓	↑	↓	↓	↓

RIGHT (art. cor. dextra).

	10	11	12	23a	23b	25	36	37	40	41	43	56	X
I	↓	=	↓	↓	↓	↓	↓	↓	↓	↓	↓	=	↓
II	↑	↑	↓	↓	=	↓	↓	↓	↑	↓	=	↑	↑
III	↑	↑	↑	↑	↑	↓	↑	↑	↑	↑	↑	↑	↑

L + R art. cor. dextr 7 weeks after ram. desc. ant.

	6
I	↓
II	↓
III	↑

In accordance with the rule of Einthoven (II − I = III), which is applicable to all types of curves, an S-T deviation must always appear in at least two leads. Further, according to the scheme of the equilateral triangle[18, 24, 25] which may also be applied to the monkey as has been shown before,[7] *a displacement* in a certain direction and of a certain magnitude *in any one lead can have a very widely divergent significance, depending on the displacement observed at the same time in the other leads.* For instance, it is a very incomplete definition of such an S-T deviation to say only that it was directed upward in Lead I. All electrical potential differences the direction of which in the heart makes an angle with the horizontal varying from +90° through 0° to − 90° could give such a deviation so that, as far as electrical relationships are concerned, cases showing such S-T deviation could differ by almost 180° from one another. The same applies to cases in which, for instance, an upward displacement in Lead III occurs. Potential

differences in the heart both from +30° to +90° left and from +90° via 180° to –150° right could give such changes in Lead III. Here, too, there is a play of about 180 degrees.

It will be clear, therefore, that the study of the S-T deviation in only one lead, as sometimes found in literature,[26, 27, 28] cannot be regarded as complete. It is advisable to consider this phenomenon in at least two of the three leads *quantitatively.*

We may try to determine in that connection both the direction and the magnitude of the potential differences existing in the heart during the tracing of the S-T deviation. We shall not discuss in this article the manifest magnitude at maximum development although a study of the possible relation between it and the size and place of the heart lesions induced would undoubtedly be justified.

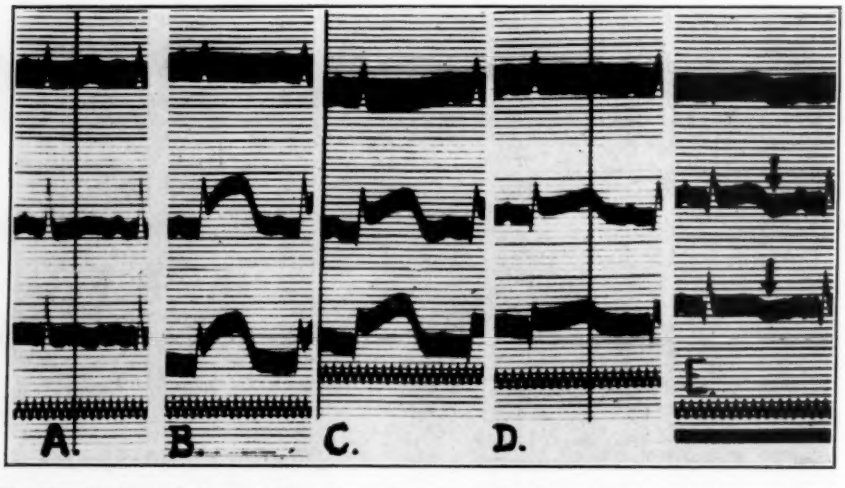

Fig. 5.—Monkey 51 L. *A*, before operation; *B*, 28 min., *C*, 33 min., *D*, 108 min., and *E*, 33 days after ligation of the ramus descendens anterior.

For the moment we shall limit ourselves to determining *the direction.*

Pardee[29] once suggested the possibility of a directional S-T displacement after coronary obstruction; Wilson and his associates[30] studied a possible direction and magnitude in semidirect leads after burning a part of the heart; however, both made, as far as we know, no quantitative measurements.

The direction of the manifest potential difference in the heart may be determined at any chosen part of the S-T deviation, as well as at any chosen part of a normal electrocardiogram.[18] In many curves, indeed, for measuring the direction of the deviation, it is immaterial what series of synchronous points of the S-T segment are taken. For instance it will be seen from Fig. 5 that during the entire course of the S-T segment the electrical axis is directed perpendicularly to Lead I (+90°).

For reasons that will be discussed later, we have limited ourselves to measuring the direction of the electrical S-T axis existing at the point of the beginning of the S-T deviation in a given complex, and, as will be described later in detail, as far as possible, at that time after the operation at which the deviation had reached its maximum development. Heretofore the S-T displacement was measured at the point at which the S-T segment springs from the QRS complex, or, if in our opinion the measurement could thereby be made more accurately, a point as near it as possible. In order to reduce errors of measurement to a minimum the direction was determined from the two leads in which the deviation was largest.

Table III gives the results of the measurements, constructions and calculations expressed as angle α of the triangle scheme, which, as has already been said above, is applicable to the monkey.

TABLE III

DIRECTION OF THE ELECTRICAL S-T AXIS IN DIFFERENT MONKEYS AFTER LEFT (L) AND RIGHT (R) LIGATION

MONKEY	CURVE NUMBER	DEVIATION IN MM. I	II	III	ANGLE α CONSTRUCTED	CALCULATED
4 L A	80	(− 5.9)	−12.8	− 6.9	−118°	−117°
B	142	+ 1.9	+ 1.1	(− 0.8)	+ 5°	+ 5°
5 L	171	+ 5.0	(− 1.9)	− 6.9	− 46°	− 45°
6 L	182	− 1.5	(+ 1.0)	+ 2.5	+127°	+127°
6 L+R	213	− 1.8	− 1.5	(+ 0.3)	−160°	−160°
9 L	276	+ 1.2	+ 2.4	(+ 1.2)	+ 60°	+ 60°
15 L	536	=	+ 6.0	+ 6.0	+ 90°	+ 90°
16 L	543	(− 0.4)	+ 2.1	+ 2.5	+ 98°	+ 99°
17 L	558	+ 1.9	(− 1.0)	− 2.9	− 51°	− 50°
19 L	620	(− 1.3)	+ 6.2	+ 7.5	+100°	+ 99°
35 L	1027	=	− 5.0	− 5.0	− 90°	− 90°
44 L	1094	+ 1.0	(− 0.5)	− 1.5	− 49°	− 49°
49 L	1140	+ 3.0	(− 0.6)	− 3.6	− 39°	− 39°
51 L	1164	=	+ 3.4	+ 3.4	+ 90°	+ 90°
52 L	1188	− 1.0	− 1.5	(− 0.5)	−131°	−131°
53 L	1199	(+ 0.5)	− 0.5	− 1.0	− 60°	− 60°
AG L	AG *B*	+ 7.6	(+ 3.5)	− 4.1	− 3°	− 3°
10 R	343	(− 4.7)	+ 5.5	+10.2	+117°	+117°
11 R	410	=	+ 1.0	+ 1.0	+ 90°	+ 90°
12 R	443	− 1.6	(− 0.6)	+ 1.0	+172°	+172°
23 R A	722	− 5.5	(− 1.0)	+ 4.5	+157°	+160°
B	728	− 5.0	=	+ 5.0	+150°	+150°
25 R	752	− 2.0	− 2.5	(− 0.5)	−140°	−139°
36 R	935	− 3.0	− 1.5	(+ 1.5)	±180°	±180°
37 R	947	− 1.5	(− 0.5)	+ 1.0	+169°	+169°
40 R	981	− 1.0	(+ 1.0)	+ 2.0	+120°	+120°
41 R	986	− 2.4	− 1.9	(+ 0.5)	−161°	−161°
43 R	1074	− 1.2	=	+ 1.2	+150°	+150°
56 R	1218	=	+ 1.0	+ 1.0	+ 90°	+ 90°
X R	1240	− 1.6	(+ 1.1)	+ 2.7	+127°	+126°

In composing this table, construction was carried out before the results of the calculations were known, by pointing off the measurements (e.q., multiplied 5, 10, or 20 times) on a schema similar to that described by Carter, Richter, and Greene.[31] Calculations were made, using the table of Einthoven, Bergansius, and Bytel.[32] This latter is more accurate, but more time consuming. As shown in our table, the errors

made by construction are very small, and in our opinion, for practical purposes including clinical use, insignificant. The measurements were made on the curves enlarged fifteen times by projection. In each lead in three successive complexes the distance of the origin of the S-T segment from the diastolic line was measured three times. In the table the number for each lead in this way represents the average of nine measurements. For practical purposes measurements with a magnifying glass would be sufficient in many cases. In order to reduce errors of measurements to a minimum, those two leads in which the deviation was greatest were selected. For each monkey, for the same reason, those curves were taken in which the deviation was, as far as possible, at its maximum development. The numbers in parentheses were not actually measured, but calculated according to Einthoven's rule.

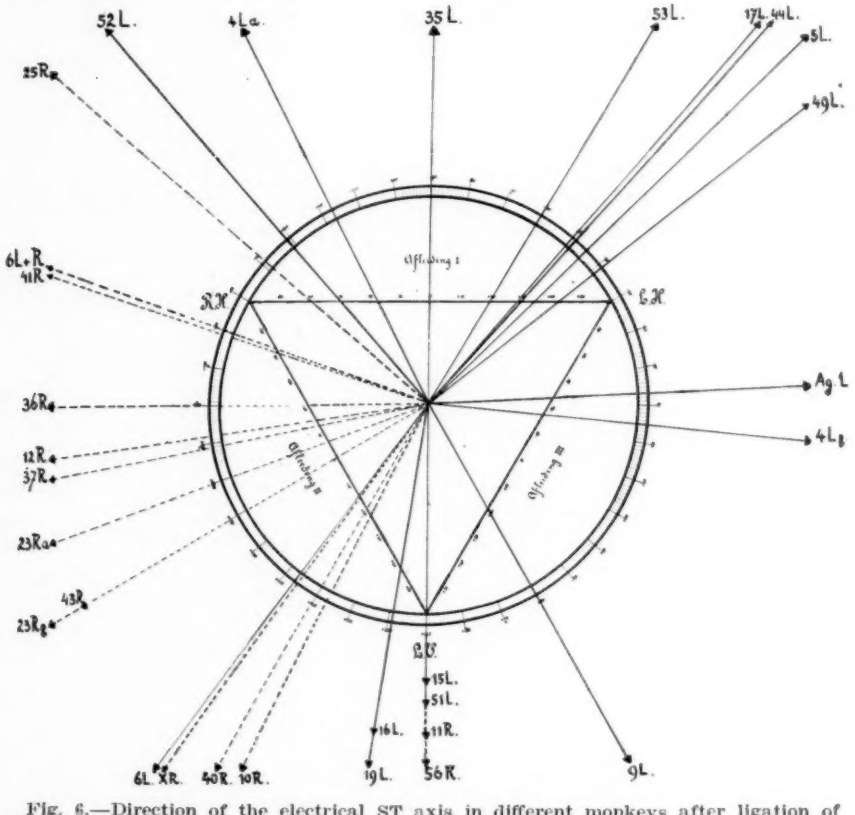

Fig. 6.—Direction of the electrical ST axis in different monkeys after ligation of the ramus descendens anterior (—) and of right coronary artery (_ _). Further details in text.

The results are also recorded in Fig. 6 in which the numbers of the monkeys concerned are also given with "L" and "R" to designate whether the ligation was left or right.

From Fig. 6 it will be seen that the S-T axes in cases of right and left ligations overlap only in a very small area (the sector from +90° to +127°) while over the entire remaining area each takes its own field, the right monkeys the right field (+127° via 180° to –139°) and the left monkeys the left field (+90° via 0° to –131°).

In general, therefore, we get the impression that, at least preponderatingly, *the electrical axis of the S-T deviation tends to point in the direction of the distribution of the ligated artery; in the direction,* that is to say, *of the developing heart lesion.*

If the monkey lives long enough, in our experience at least two days, this developing heart lesion will, as a rule, manifest itself later morphologically although in all probability never in its original size, since, depending on the possibilities of collateral circulation, some repair will take place at the periphery, as described in other animals.[33, 34] It is probable that these possibilities will be greater in animals that were originally healthy than, for instance, in patients with pathologically altered heart vessels.[35, 36]

TABLE IV A

SITE OF LESIONS FOUND MICROSCOPICALLY IN LEFT MONKEYS

MONKEY	SURVIVAL AFTER OPERATION	SITE OF LESION*
4 L	6 mo.	Anterolateral part of L. V., middle and apex. Also septum lesion.†
6 L	7 wk.	Anterolateral part of L. V., middle and apex; at apex crossing over to R. V. Also septum.
9 L	5½ mo.	Lateral part of L. V., middle and apex. Also septum.
17 L	2 days	Anterolateral part of L. V., middle and apex. No septum lesion.
19 L	2 mo.	Beginning midway in sulcus interventr. ant., enlarging in apical direction, at apex occupying whole ant. and lat. part of L. V., and ant. part of R. V. Also septum.
44 L	1½ mo.	Anterolateral part of L. V., only at middle, not reaching base or apex. No septum lesion.
49 L	5 days	Anterolateral part of L. V., principally at middle, less at apex. No septum lesion.
51 L	1 mo.	Exclusively at apex, occupying anterolateral part of L. V. and whole apical part of R. V. Also septum lesion.
53 L	1 mo.	Anterolateral part of L. V., principally at middle, a little at apex, not at base. Also septum lesion.

*L. V. = left ventricular wall; R. V. = right ventricular wall.
†Septum lesions described later. See also Fig. 11.

Lesions were found in the monkeys shown in Tables IV A and IV B. In all these animals, as well as in the others described, the microscope confirmed the efficiency of the ligation.*

We shall discuss further the site of these lesions† in Part III of this paper.

*The microscopic examination of the hearts and also the larger part of the autopsies were carried out under the personal supervision and control of Dr. H. Müller, Director of the Pathological Institute of the Medical School at Soerabaja, and during the operative part of our researches acting-director of the Pathological Institute at Batavia, and with the cooperation of our student assistant, J. H. Jansen. It is a pleasure to express our thanks for their valuable assistance.

†The microscopic details of the lesions will not be discussed. The position and extent of the lesions were confirmed by Dr. H. Müller, and their boundaries were drawn under his supervision by J. H. Jansen, as they showed in heart sections in 7 equidistant planes, lying perpendicularly to the heart axis, beginning at the base, ending at the apex.

The following method was used for the microscopic examinations: Fixation of the heart in 5 per cent formalin; organ cut into slices of about 1 cm. perpendicularly to axis and embedded in ceducol; sections made of 30 microns. At least each tenth section was studied microscopically, being finally stained with eosin and hematoxylin.

TABLE IV B

SITE OF LESIONS FOUND MICROSCOPICALLY IN RIGHT MONKEYS

MONKEY	SURVIVAL AFTER OPERATION	SITE OF LESION*
10 R	6 mo.	Wall of R. V., at base larger than at apex, extending to posterior side and post. part of septum.† At apex also extending to posterior part of L. V.
11 R	6 mo.	As 10 R, only not extending to posterior apical part of L. V. Also septum lesion.
12 R	5½ mo.	Lateral wall of R. V. except the apex. No septum lesion.
14 R	4 mo.	Middle anterior third of R. V., not reaching base or apex. No septum lesion.
31 R	1 mo.	Exclusively small anterior part of R. V. near conus arteriosus. No septum lesion.
41 R	4 days	Anterior, lateral, and posterior part of R.V., especially at middle and at base. Also septum lesion.
43 R	1½ mo.	Exclusively lateral part of R. V., principally at the base, not reaching the apex. No septum lesion.
56 R	3 wk.	Lateral middle part of R.V., not reaching base or apex. No septum lesion.

*L. V. = left ventricular wall; R. V. = right ventricular wall.
†Septum lesions described later. See also Fig. 11.

We have measured the direction of the S-T deviation in the way described above, as far as possible, at that time after the operation at which it had reached its maximum development.

If the measurements were made at other times, it appeared that the manifest magnitude was different but that the direction of the electrical axis varied very little, in our experience as a rule not more than about 20°, often less. This is a variation which approaches in magnitude the possible errors in measurement. Another factor may perhaps be the influence of the respiratory phases since it is impracticable to make all measurements in one given respiratory phase.

Figure 5 gives an example of an S-T axis which kept its direction of +90° for thirty-three days. The rather small oscillations, which were observed in those cases where the S-T deviation existed longest, are given in Table V.

TABLE V

SEE TEXT

MONKEY	DIRECTION OF ST AXIS		DIFFERENCE	
	IN MAXIMAL DEVELOPMENT	LATER	IN DIRECTION	IN TIME
9 L	+ 60°	+ 35°	25°	5 mo.
19 L	+ 99°	+ 90°	9°	2 wk.
44 L	− 49°	− 47°	2°	1 mo.
51 L	+ 90°	+ 90°	0°	1 mo.
53 L	− 60°	− 79°	19°	1 mo.
10 R	+117°	+150°	33°	3 mo.
43 R	+150°	+150°	0°	12 days
56 R	+ 90°	+ 90°	0°	1 wk.

We shall discuss later Monkey 4 L (A and B) which seems to be an exception to this rule.

Monkey 6 after the left ligation (6 L) showed a mixed type (+127°), but after the second operation seven weeks later, when a right ligation was also done, it showed a right type (–160°). In this case (6 L + R), therefore, it is probable that the artery last ligated or the latest lesion to develop impressed its influence on the electrocardiogram (Part II, Fig. 12).

Monkey 23 R showed for a short time an S-T direction of +160° (type A), afterward of +150° (type B), the S-T segment again becoming isoelectric in Lead II (Part II, Fig. 15).

In regard to *the secondary changes in the ventricular electrocardiogram,* which arise later, we must state that in practically all the monkeys

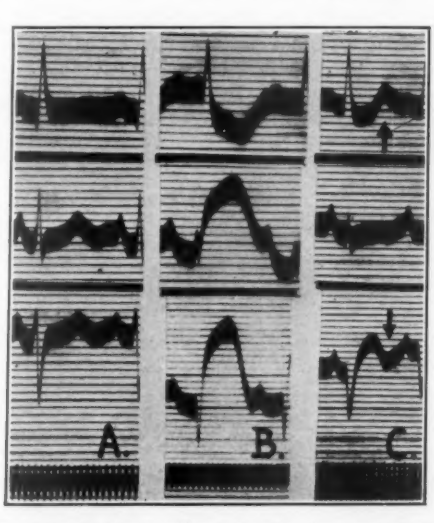

Fig. 7.—Monkey 10 R. *A*, before operation; *B*, 63 min., and *C*, 3 weeks after ligation of right coronary artery. See also Part II, Figs. 3, 4, 5, and 10.

(with the exception of those in which fibrillation rapidly ensued) we observed to a greater or less degree the phenomenon first described by Parkinson and Bedford,[35] namely the development of an after-wave during the reduction of the S-T deviation and developing in the opposite direction.

Examples of this are shown in Fig. 7 (segment *C*) and several other of our illustrations (Figs. 5*E*, 8*C*, 9*D*, 10*D*, 12*C*, and 16*D*).

The last mentioned authors have shown that this secondary after-wave developed in such a way that its apex just coincided with the end of the previously existing ventricular complex, in other words that the development of this secondary wave was accompanied by a prolongation of the (electrical) systole. Our curves confirmed this statement.

If now for the sake of brevity we call the electrocardiogram obtained immediately after the ligation (in which as a rule the S-T deviation is already present, but the secondary after-wave still absent) the primary coronary electrocardiogram (prim.) and the curve in which the after-wave has developed the secondary coronary electrocardiogram (sec.), it must be noted that the former seldom shows any prolongation or shortening of the ventricular systole in comparison with the original electrocardiogram (orig.), while the latter almost without exception shows a prolongation, even when account is taken of possible changes in the heart rate.

Examples of this are given in Table VI.

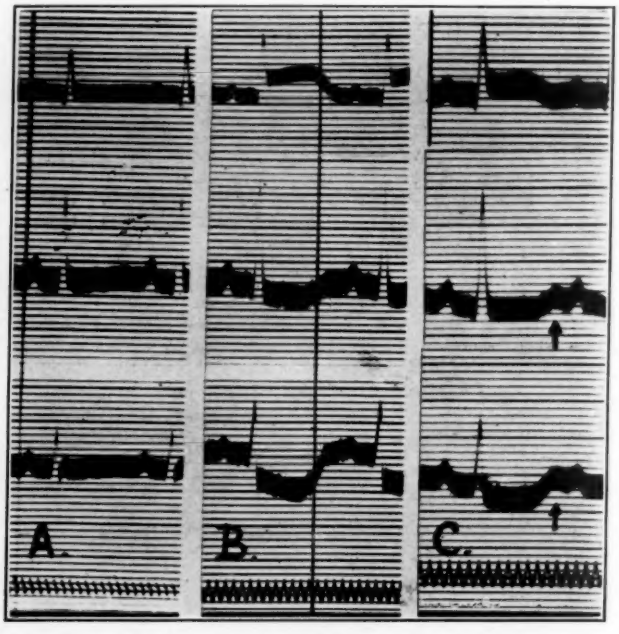

Fig. 8.—Monkey 49 L. *A*, before operation; *B*, 63 min., and *C*, 3½ hours after ligation of the ramus descendens anterior.

In Part III of this paper we shall consider again the subject of this time relationship.

It must still be pointed out that in making these time measurements attention must be paid to the lead in which they are most clearly to be seen. It can even happen after ligation that in one lead the ventricular complex more or less retains not only its length but also its form, whereas in the other leads both prove to be considerably altered. An example of this is shown in Part II (Fig. 15 there), in which in the secondary coronary electrocardiogram of Monkey 23 R the ventricular complex lasted 0.26 second in Leads I and III, and at the same time 0.23 second in Lead II. The final swings in Leads I and III so nearly compensated one another that in Lead II the string returned to the diastolic line earlier than in the other leads. Lead II, except for the fact that a nodal rhythm developed, had the same form as far as the ventricular complex is concerned as before the operation, while in Leads I and III this complex markedly changed.

QRS Changes.—In addition to the electrocardiographic changes described above, *changes in the QRS complex* were observed in several of the monkeys.

In a detailed study of this complex and the attributing of definite value or significance to changes observed in it, the question must always be asked whether in any given instance technical or instrumental errors are playing a part (a still greater liability in recording the very rapid electrical variations of the monkey heart), or whether either displacements of the heart or differences in the respiratory phases may be responsible.

TABLE VI

Examples showing prolongation of ventricular complex in secondary coronary electrocardiogram (sec.) and absence thereof in primary coronary electrocardiogram (prim.) in comparison with the original electrocardiogram (orig.).

MONKEY	TYPE ECG	LENGTH VENTR. COMPL.	HEART RATE	MONKEY	TYPE ECG	LENGTH VENTR. COMPL.	HEART RATE
4 L	orig.	0.15	236	51 L	orig.	0.17	240
	prim.	0.15	236		prim.	0.17	222
	sec.	0.21	214		sec.	0.19	231
5 L	orig.	0.15	260	10 R	orig.	0.18	196
	prim.	0.16	245		prim.	0.18	200
17 L	orig.	0.22	158		sec.	0.21	191
	prim.	0.24	143	11 R	orig.	0.17	214
	sec.	0.26	143		sec.	0.21	194
35 L	orig.	0.18	240	36 R	orig.	0.19	188
	prim.	0.19	192		prim.	0.18	188
	sec.	0.20	201	43 R	orig.	0.22	188
44 L	orig.	0.19	204		prim.	0.22	176
	prim.	0.19	204	56 R	orig.	0.16	206
	sec.	0.19	195		prim.	0.16	206
49 L	orig.	0.18	214		sec.	0.17	214
	prim.	0.18	203				
	sec.	0.21	210				

Particular attention was paid to these considerations.

In our opinion the following QRS changes (Table VII) may be regarded as resulting from the interruption of the coronary circulation and the internal changes in the heart caused thereby. Since a possible connection with septum lesions appeared, the findings in that direction are also given (see also Fig. 11).

These observations are summarized in Table VIII.

We regard these observations as too small in number to allow us to draw conclusions from them with certainty as to differences between the results of left and right ligation.

Some connection between QRS changes and S-T displacement might be deduced from the fact that in all cases in which there was an increase in the Q-wave in any given lead, S-T ascended in the same lead (see also Wilson and his associates[33] and Parkinson and Bedford[35] and Fig. 9), while in all cases in which the Q-wave was reduced the corresponding S-T descended.

However, there is no direct parallel, since the QRS changes are not always maximal at the time when the S-T displacement is maximal, but

often later, during the recession of the deviation and the development of the secondary after-wave (see, for instance, Fig. 5). Moreover, the S-T deviation and after-wave could develop without there being any QRS change (see Figs. 10 and 16), but, on the other hand, we never saw a change in the QRS complex in a monkey which did not also show a displacement of the S-T segment. For this reason we are not justified in considering the prolongation of systole, which is practically always observed during the existence of the QRS change, as having a relationship especially or only to this latter change.

TABLE VII

DATA CONCERNING QRS CHANGES

MONKEY	INCREASED OR DEVELOPED	DECREASED OR DISAPPEARED	FIRST SEEN AFTER OPERATION	DURATION OF LIFE AFTER OPERATION	SEPTUM LESIONS FOUND*
4 L	Q_1	–	5 mo. (4 B)	6 mo.	yes
6 L	Q_2, Q_3	–	7 wk.	7 wk.	yes
9 L	Q_1, Q_2	–	35 min.	5½ mo.	yes
16 L	Bundle-branch block		5 min.	13 min.	no
19 L	S_2, S_3	–	45 days	2 mo.	yes
51 L	Q_2, Q_3	–	33 min.	1 mo.	yes
53 L	S_2, S_3	–	20 days	1 mo.	yes
6 L+R (after R lig.)	S_1, S_2	Q_2, Q_3	10 min.	7 wk. after L. 2 hr. after R.	yes (probably from L)
10 R	–	Q_1	57 min.	6 mo.	yes
11 R	Q_1?	Q_2	3½ mo.	6 mo.	yes
36 R	S_2	Q_2	52 min.	6 hr.	no
37 R	S_1, S_2	Q_1, Q_2	17 min.	1 hr.	no
41 R	S_1, S_2	Q_1, Q_2	26 min.		
	Q_2, Q_3	S_1, S_2	1 day	4 days	yes

*See also Fig. 11.

TABLE VIII

SUMMARY OF THE RESULTS TABULATED IN TABLE VII*

	TOTAL NUMBER OF MONKEYS IN WHICH:											
	Q_1		Q_2		Q_3		S_1		S_2		S_3	
	+	–	+	–	+	–	+	–	+	–	+	–
After L. ligation	2	0	3	0	2	0	0	0	2	0	2	0
After R. ligation	0(1?)	3	1	5	1	1	3	1	4	1	0	0

*+ = development or increase.
– = disappearance or decrease.

At this time we must be satisfied with saying that undoubtedly the most important prolongations appeared to be connected with the presence of the after-wave and not with that of the QRS changes. If the latter appeared before the after-wave then in one case (Monkey 36 R), with the heart rate unchanged, the systole even appeared to be shortened, whereas whenever there was an after-wave without any change in the QRS complex, systole was prolonged.

Summarizing, we may say that S-T deviations were repeatedly seen without changes in the QRS complex, at least in that part of it which

remained visible; that QRS changes were never observed without S-T deviations, although as a rule they became apparent only when the S-T changes were decreasing, and that no definite connection between a QRS change in itself and an altered duration of systole could be observed.

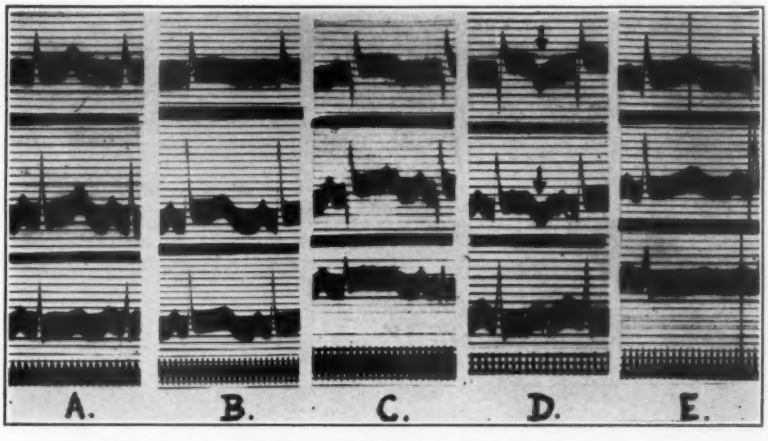

Fig. 9.—Monkey 9 L. *A*, before operation; *B*, 35 min., *C*, 1 day, *D*, 34 days, *E*, 5½ months after ligation of the ramus descendens anterior. Example of S-T deviation with changes in QRS.

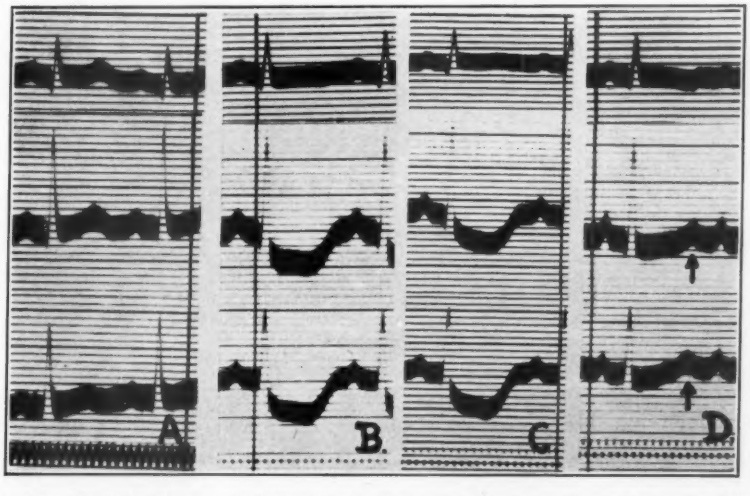

Fig. 10—Monkey 35 L. *A*, before operation; *B*, 13 min., *C*, 88 min., *D*, 6 hours after ligation of the ramus descendens anterior. Example of ST deviation without changes in QRS.

Although as a rule the course of development of a possible QRS change proved to be slower than that of the coexistent S-T deviation, we could not determine with certainty from our curve material which of the two disturbances remained longer in evidence. We never observed late QRS changes unaccompanied by other changes, as Wilson

and his associates[33] did in man. There was in our monkeys always a residual S-T deviation or after-wave still showing.

In the literature QRS changes are often connected with function disturbances of the intraventricular conduction system, especially in the septum.[37-40] We requested the pathologist, therefore, to pay attention particularly to the septum. In Table VII we have already stated in which of our animals showing QRS changes septum lesions were found. That they were not visible in Monkeys 16 L, 36 R, and 37 R (also 6 L + R especially after right ligation) may be due to the fact that these animals survived the operation only so short a time. There may well have been functional disturbances in the septum in these cases.

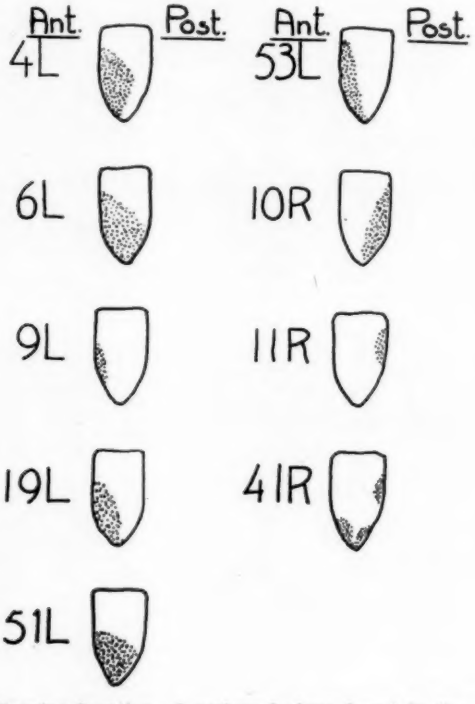

Fig. 11.—Showing location of septum lesions found in the monkeys.

Figure 11 shows in which monkeys septum lesions were found and where they were located.

In general these lesions were more severe in the left monkeys than in those in which right ligation had been performed, which coincides with what might be expected from the description of the circulation relations in the septum given before. After left ligation the lesions were principally below and anterior; after right ligation, if present at all, prinicipally in the middle portion posterior and of comparatively small size.

If we combine the results shown in Fig. 11 with the data of Table VII, we come to the following conclusions.

In thirteen monkeys QRS changes were present. In nine of these also septum lesions were found microscopically. In the remaining four (including Monkey 6 L + R after right ligation) no such morphologically visible lesions were to be expected because these monkeys survived too short a time. In all other monkeys used in these experiments, neither QRS changes nor morphologically visible septum lesions were present, although there were among them seven animals which survived the operation considerably longer than two days (the minimum interval after the ligation, in which lesions became recognizable).

Therefore, we regard it as very probable that there is a connection between QRS changes and function disturbances of the septum, at least in monkeys.

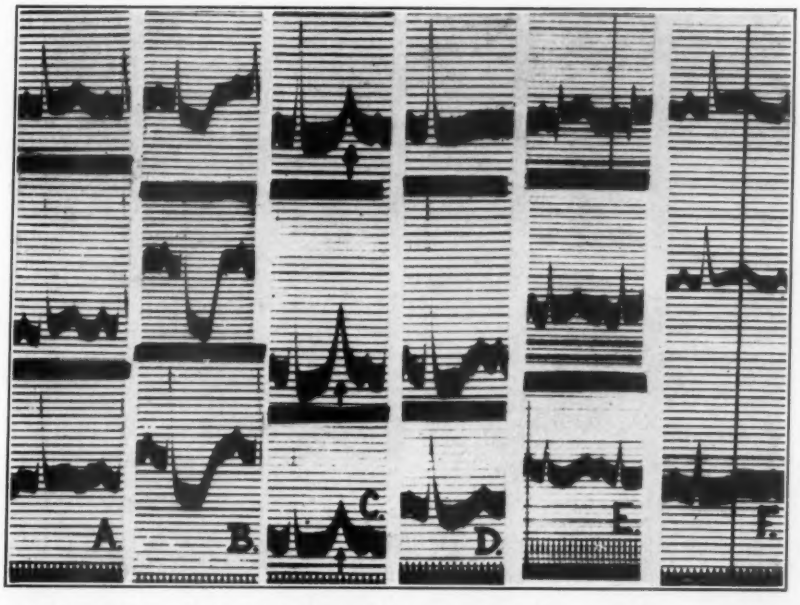

Fig. 12.—Monkey 4 L. *A*, before operation; *B*, 50 min., *C*, 1 day, *D*, 8 days, *E*. 5½ months, *F*, 6 months after ligation of ramus descendens anterior. *B* is described in text as type A, *E* as type B of this monkey.

Let us now consider on the basis of the following extracts from our work to what extent the animals which survived the operation longest again showed their original electrocardiogram. In other words, what were *the last remaining traces of the changes in the ventricular complex?*

It may be noted beforehand that our observations show that in general an electrocardiogram which after ligation had once become altered never quite returned to normal. Changes remained both in the configuration and in the time relationships. In this connection, however, it should be pointed out that none of our animals was allowed to survive the operation longer than six months.

Monkey 4 L.—After six months the S-T segment in Leads I and II was too high, in Lead III slightly too low. The length of systole had risen from 0.15 to 0.20 sec., the heart rate had fallen only from 236 to 208. The peculiarity of this animal was the development of a second type of S-T deviation, observed about five months after the operation. It seems possible that the first deviation (4 *A*:−117°), observed directly after the operation, is connected with the septum lesions found in this monkey; the second deviation (4 *B*:+5°) with the heart aneurysm that proved to be present in the so-called anterior wall of the left ventricle about one-third of the length of the ventricle from the apex, adjoining the septum. It should, however, be noted that the QRS change (Q_1) was observed only in Type 4 *B* (see Figs. 12 and 13).

Monkey 9 L.—As shown in Fig. 9 the S-T segment was still too high, especially in Leads I and II, five and one-half months after the operation. Of interest was the development of Q_1 and Q_2, of which Q_1 appeared first and remained the longer. Be-

Fig. 13.—Monkey 4 L. Aneurysm of left ventricular wall, involving anterior part of septum, 6 months after ligation of the ramus descendens anterior.

tween the first and last curve there was, besides the Q_1 and the S-T deviation, this further difference that in the latter, in spite of a reduced pulse rate, the systole must be regarded as relatively prolonged (first curve 0.15 sec., with a frequency of 220, final curve 0.20 sec. with a frequency of 166).

Monkey 19 L after two months still showed traces of the after-wave, as well as a definite S_3, which was previously not present, and an increased S_3. The systole appeared to be prolonged in the final curve which, however, showed too many incidental vibrations for accurate measurement.

Monkey 10 R after five months still showed traces of the original S-T deviation, as well as a definite after-wave and a prolonged systole at a higher heart rate (originally 0.18 sec. with a frequency of 196, finally 0.20 sec. with a frequency of 218). Furthermore there were changes in the QRS complex, Q_1 was still absent. (See for this monkey Fig. 7 and in Part II, Figs. 3, 4, 5, and 10.)

Monkey 11 R.—After five months the electrocardiogram at first sight closely resembles the original. The T-wave is, however, somewhat changed in form, the isoelectric part between R and T is prolonged and in Lead III is convex and followed by a negative T_3, remains of the after-wave perhaps. The systole is relatively shortened, the pulse less frequent (originally 0.17 sec. and 214, final curve 0.17 and 171). Q_1 seems still slightly increased.

Monkey 12 R.—There appeared after five months in Leads I and II a high sharp positive T-wave following a negative S-T segment in both leads and a negative T_3 following a positive S-T segment in Lead III. The length of systole was shortened from 0.19 to 0.15 sec., the pulse rate, however, had risen from 204 to 252. (See for this monkey Fig. 14, and Part II, Fig. 6.)

Monkey 14 R.—The final curve taken after four months showed too many incidental vibrations for detailed study. In general the electrocardiogram of this

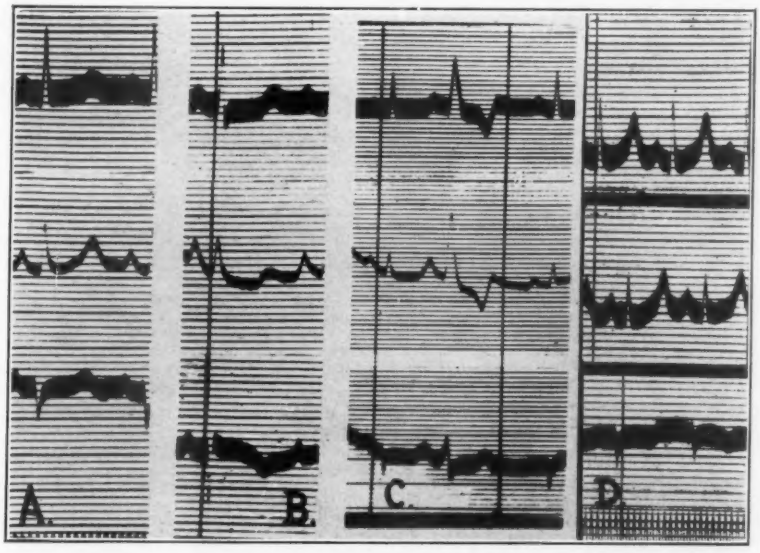

Fig. 14.—Monkey 12 R. *A*, before operation; *B*, 85 min., *C*, 1 day, and *D*, 5 months after ligation of right artery. In *C* extrasystole from right ventricle, apical part, interfering with P-wave. See also Part II, Fig. 6.

animal appeared not to be noticeably altered during the entire course of the observations, a fact which we ascribe to the frontal position of the lesion, as will be explained in Part III of this paper.

Monkey 31 R.—After about one month there was a markedly negative T_1 and positive T_2. There had been formerly no definite S-T deviation. The visible lesion was, as in 14 R, situated well to the front (see also Part III). It was limited to the conus arteriosus, in all probability because only the corresponding small branch of the right artery had been ligated. Apparently an after-wave had developed without any clear ST deviation preceding. Systole was definitely prolonged (originally 0.18 sec. and pulse rate 194, finally 0.21 sec. and 206).

Monkey 43 R (see Fig. 15).—After one and one-half months the electrocardiogram shows similarities with the original curve, although the T_3, perhaps not unconnected with the small negative after-wave formerly developed in III (Fig. 15 *C*), is not yet positive. In view of the fact that P begins before the end of T no measurements of the length of systole are possible.

Monkey 56 R (see Fig. 16).—After three weeks the S-T deviation had disappeared, but there was still a clearly observable after-wave present especially in Leads II and III. Systole was prolonged (originally 0.16 sec. and pulse rate 206, finally 0.17 sec. and 214).

Before passing on to Part II of this paper, we shall discuss briefly two special cases in which the electrocardiogram reminded us of that found after ligation.

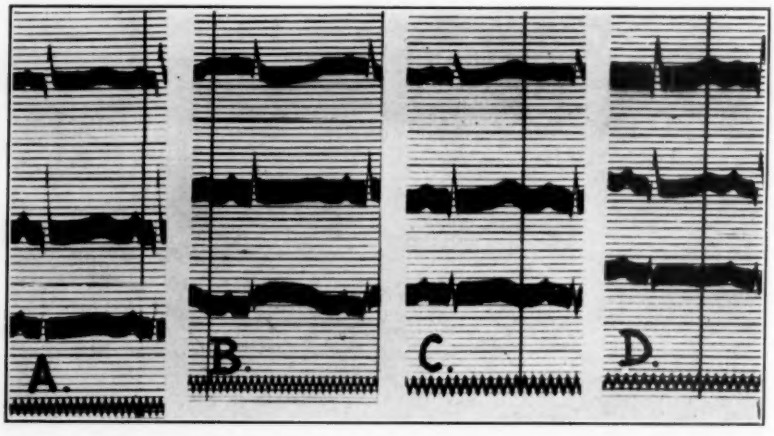

Fig. 15.—Monkey 43 R. *A*, before operation; *B*, 75 min., *C*, 9 days, *D*, 1½ months after ligation of right artery.

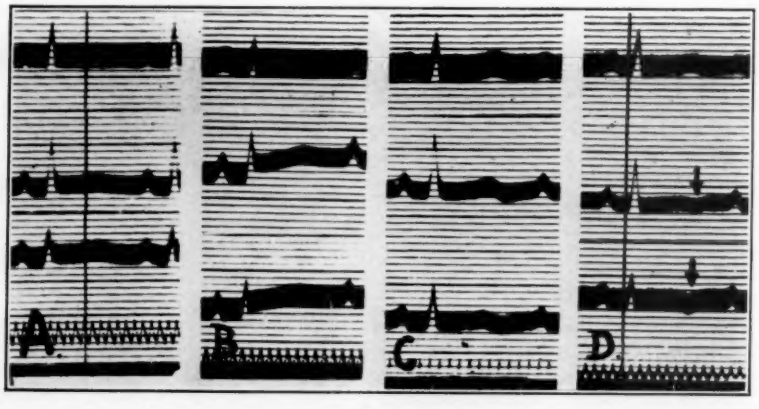

Fig. 16.—Monkey 56 R. *A*, before operation; *B*, 2 hours, *C*, 2 weeks, and *D*, 3 weeks after ligation of right artery.

1. It has been mentioned[41] that death following *air embolism* might in many cases be due to the closing off of one or more of the coronary arteries or some of their branches, and in such instances electrocardiograms were obtained closely resembling the "coronary type."

We injected into the femoral vein of Monkey 16 B several cubic centimeters of air. Within a couple of minutes (see Fig. 17) there appeared a deviation of the S-T segment. There was a temporary nodal rhythm with extrasystoles originating in

the right apex. The heart later returned to a slowed sinus rhythm with an increase of the S-T deviation. Finally, after fifteen minutes, ventricular fibrillation was visible in the string movements. The S-T axis pointing at an angle of +106° (mixed field) gave no definite evidence in favor of left or right obstruction. The apparently localizing extrasystoles might have been due to an increased resistance in the

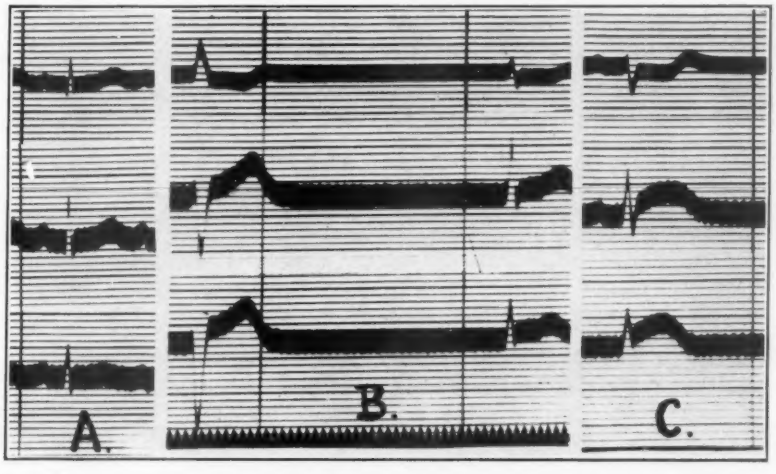

Fig. 17.—Monkey 16 B. *A*, before experiment; *B*, 5 min., *C*, 10 min. after injection of air into vena femoralis. In *B*, note extrasystole of right apex type and nodal rhythm.

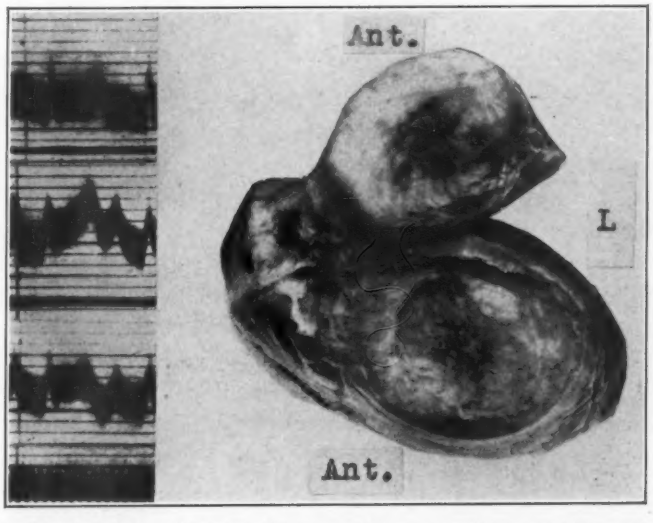

Fig. 18.—Monkey 27. Electrocardiogram before operation showing S-T deviation in Leads II and III, and heart showing spontaneous disease, visible as white patches in musculature.

pulmonary circulation, in which case probably both coronary arteries would get too little blood. Dr. Müller performed the autopsy and found the right heart filled with air. Undoubtedly there had been a disturbance of the coronary circulation due to some cause operating within the cardiovascular system. The rapid appearance and subsequent disappearance of the nodal rhythm also points in this direction.

It seems useful to report this case since it supports our opinion that similar electrocardiographic changes obtained by ligation of the arteries are not dependent on damage to nerves that accompany the arteries. As a matter of fact, others[19] have obtained similar changes in the electrocardiogram in dogs when the occlusion of the arteries had been produced from within with lycopodium. With the single exception of air embolism, described above, we were not able to use successfully in our monkeys methods by which the arteries are obstructed from within, although in some animals efforts were made to pass sounds from the carotid into the coronary orifices.

2. The second special case concerned a *pathological monkey heart.*

In all our healthy monkeys we found the S-T segment constantly isoelectric. When, therefore, in Monkey 27, as an exception, even before operation, the curve reproduced in Fig. 18 was found, in which the S-T segment in Leads II and III was abnormally high (S-T direction +90°), the operation was not performed and the animal was immediately killed for investigation.

The following report was received from Dr. H. Müller: "In addition to changes in the liver and spleen, white patches were clearly visible even macroscopically in the heart muscle at the apex of the left and right ventricles. Microscopically there were peculiar changes in the muscle fibers in these regions, which were swollen by large vacuoles. There were signs of muscle degeneration and a few indications of regeneration. A toxic infectious origin seems probable."

SUMMARY

Reasons are given why monkeys offer many advantages over other animals for experimental heart research, especially for electrocardiographic research, in spite of the fact that the anatomical structure of their coronary system sometimes differs from that of man. This anatomical structure and its relationship to that of man are described in the Javanese monkey *Macaca irus.* After the normal electrocardiogram and the influence of various incidental factors on it had been studied, coronary vessels were ligated in these monkeys. In seventeen of the animals described, the anterior descending branch of the left artery (L) was tied off and in fourteen the right artery (R). In one monkey the right artery was ligated seven weeks after the anterior descending branch of the left. The electrocardiograms were recorded in the customary Leads I, II, and III, mostly simultaneously. S-T deviations were shown by all monkeys, except two left monkeys which fell immediately into ventricular fibrillation, and two right monkeys which afterward were shown to have exclusively frontal lesions. The S-T deviation appeared within ten minutes, reached its maximum in about one hour, and disappeared in an average time of one month. The S-T deviation must always be observable in at least two leads; its study in only one lead is of but little value. The direction of the S-T deviation

(the electrical S-T axis) was determined, according to the principles of the equilateral triangle, by quantitative measurements in at least two leads. This direction proved to point after left ligation preponderatingly to the left, and after right ligation preponderatingly to the right. There was a small mixed sector, in which the S-T axes of left and right monkeys were shown to overlap. During development of the S-T deviation systole is usually not prolonged. Among the secondary changes in the ventricular electrocardiogram there was often observed an after-wave in a direction opposite to that of the preceding S-T deviation. This was accompanied by a prolongation of systole. Changes in the QRS complex are described in thirteen animals. No definite direct relation between those changes and an altered duration of systole could be found. There appeared to be a probable connection between those changes and septum lesions. An electrocardiogram that after ligation had once changed never returned within six months to its original form completely. Two special cases (one of air embolism and one of a spontaneous heart disease) are described, in which in the monkeys concerned the electrocardiogram resembled that after coronary ligation.

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THE USE OF INTERMITTENT VENOUS COMPRESSION IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE*

A Preliminary Report

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THE inadequacy of present methods in the treatment of peripheral vascular disease is exemplified by the large number and variety of methods employed. It simply speaks for the insufficiency of any one method. The various measures used to date have consisted of the following: (1) bed rest;[1] (2) physiotherapy consisting of the application of heat by baking, baths, and diathermy;[2-4] (3) postural exercises;[5] (4) elimination of all spasm-producing substances such as: (a) tobacco,[6, 7] (b) exposure to cold, (c) ergot-containing foods such as rye bread and pumpernickel;[8] (5) the use of vasodilating drugs such as: (a) theobromine,[9] (b) acetyl-beta-methylcholine,[10] (c) alcoholic beverages,[11] (d) hot drinks,[12] (e) papaverine,[13] (f) calcium,[14] (g) parathyroid hormone;[15] (6) reflex vasodilatation produced by immersion of upper extremities in hot water, such as employed in the Landis test;[16] (7) operative procedures for the production of vasodilatation, such as ganglionectomy or arterial stripping of Leriche;[17, 18] (8) intravenous injections of hypertonic solutions of either sodium chloride or buffered sodium citrate;[19, 20] (9) intravenous typhoid vaccine and other foreign proteins;[21] (10) alcohol injection of peripheral nerves;[22] (11) pancreatic extract (insulin-free);[23] (12) mechanical methods of improving circulation by alternate suction and pressure;[24] (13) femoral vein ligation.[25-32] A critical survey of the efficacy of the above methods is outside the scope of this paper.

An interesting series of experiments[33] dating back to the latter part of the nineteenth century has led to a physiological observation which hypothetically should possess a practical application to the treatment of peripheral vascular disease. We refer to the phenomenon of "reactive hyperemia." By reactive hyperemia is meant a flush or hyperemia which develops during the release of obstruction to circulation of an extremity. It has been demonstrated that this phenomenon is totally independent of nerve innervation.

In a very comprehensive study on the reaction to venous obstruction, Lewis and Grant[34] made the following observations: 1. If a pneumatic cuff be applied to an extremity and pumped up to 25 mm. of mercury pressure, an increase in the volume of the extremity, as recognized by means of plethysmographic methods, occurs within fifteen seconds. 2.

*From the Metabolic Clinic of the Israel Zion Hospital.

The degree of increase in volume is directly proportional to the increase in pressure up to 90 mm. of mercury. 3. At the end of fifteen minutes of compression, a definite increase in volume pulse occurs. 4. With the release of pressure, there is first a fall, then a rise in volume. The greater the original pressure, the greater is the secondary rise. 5. Heating the extremity accentuates the amplitude of this phenomenon. 6. This secondary rise, called a "hump," indicates that simple venous congestion may produce a vasodilatation similar to that which occurs when an occluded artery is released. 7. They believe that the release of venous congestion is associated with both active and passive vasodilatation of the arterioles. 8. The most important observations which these authors make, from the standpoint of our studies, is that there occurs, *during the release* of venous congestion, an increase in arterial flow of as much as 600 per cent, depending upon the degree and duration of applied venous congestion.

It would appear, then, that obstruction to venous flow is associated, when this obstruction is released, with an active vasodilatation of the arteries and a remarkable increase in arterial flow.

A large series of studies, both in the experimental animal and in the human, have been carried on in the past with the view of stimulating arterial flow through diseased vessels by obstructing the venous return.[25-32] The experimental procedure[28] has consisted of the simultaneous ligation of the femoral vein and artery without the eventual production of gangrene. This observation in the dog led to subsequent femoral vein ligations in humans suffering from either thrombo-angiitis obliterans or peripheral vascular sclerosis. Some workers have felt that there is a measure of value in this procedure,[31] while others have been more skeptical.[30]

On the basis of the careful studies of Lewis and Grant, it appears that the benefit to be derived from venous obstruction comes, not as a result of the obstruction per se, but from the *release* of an obstruction. It is on this basis that we feel there is a fallacy in the ligation of the femoral vein for the treatment of peripheral vascular disease.

We have attempted to alter this procedure sufficiently to incorporate the beneficial effects of venous obstruction and release by utilizing an apparatus (described in the following paper) designed to produce alternating periods of venous congestion and release of congestion.

After a preliminary trial of the application of various degrees and lengths of time of venous compression, we arrived at what appeared to be an optimal technic. We found it impracticable to apply the higher pressures which Lewis and Grant observed to produce maximal increases in circulatory flow in normal, because these levels produced considerable pain in extremities with occluded vessels and gangrene. We found, on the contrary, that sustained venous compression at 30 to 60 mm. of mercury for two minutes followed by a release of this pressure for an-

other two minutes resulted in the clinical benefits which we wish to report. The technic consisted of applying venous compression at mid-thigh, alternating with release in periods of two minutes for as long as twelve hours continuously each day.

The criteria employed in determining the effectiveness of treatment consisted of: (1) walking test; (The patient was required to walk at a rate of eleven paces per five seconds. The total distance and the time the patient was able to walk plus the time at which claudication developed were recorded.) (2) hot water immersion test (Landis); (3) oscillometric readings; (4) relief of pain; (5) healing of ulcers; (6) effect of treatment on skin temperature.

CASE REPORTS

CASE 1.— A. W., a forty-eight-year-old Jewish male, a salesman, married, was first seen Sept. 8, 1935, with a history of having had diabetes for thirteen years. Seven months before, in "breaking in" a pair of new shoes, he developed a blister over the medial surface of the head of the first right metatarsal, which subsequently became infected and had not healed up to the time of admission. He also complained of substernal pain on exertion and paresthetic symptoms in the plantar surface of the right foot. His diabetic management had consisted of dietetic restrictions up to seven months previously, and, after the ulcer had appeared, he was given 20 units of insulin twice a day. The treatment of the ulcer consisted of bed rest, during the major portion of this period, and at various times, baking and wet dressings.

Examination disclosed a middle-aged man, poorly nourished, presenting evidence of cataracts in both eyes. His blood pressure was 193/100 mm. The lower extremities showed the following: a small indolent ulcer one-quarter of an inch in diameter on the medial surface of the right metatarsophalangeal joint, with a grayish unhealthy base, surrounding redness, and slight edema of the right leg. No dorsalis pedis or posterior tibial pulsations could be obtained.

TABLE I A

HOT WATER IMMERSION (LANDIS)*

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	79.2° F.	80.2° F.	79.2° F.
After 20 minutes' immersion of hands in hot water (110° F.)	81.2° F.	85.7° F.	79.2° F.

*Foot temperatures in this and subsequent experiments were taken at the base of the first toe or as near that point as the lesion permitted.

TABLE I B

OSCILLOMETRIC READINGS

	LEFT LEG					RIGHT LEG				
Blood pressure	220	180	140	120	80	220	180	140	120	80
Dorsal pedis	0	0	0	0	0	0	0	0	0	0
Lower ⅓ leg	0	0	Tr	Tr	0	0	0	Tr	0	0
Upper ⅓ leg	0	0	Tr	Tr	Tr	0	0	Tr	Tr	0
Thigh	1	1	¾	½	½	½	½	¼	¼	Tr

The diagnosis was essential hypertension, diabetes mellitus, and peripheral vascular sclerosis with partial obstruction and chronic indolent ulcer of foot.

TABLE II

	LEFT LEG								RIGHT LEG							
Blood pressure	220	180	160	140	120	100	80	60	220	180	160	140	120	100	80	60
Dorsal pedis	0	Tr	Tr	Tr	Tr	Tr	Tr	Tr	0	0	0	0	0	0	0	0
Lower ⅓ leg	¼	¼	½	½	¼	¼	¼	¼	0	¼	¼	¼	¼	¼	Tr	Tr
Upper ⅓ leg	1½	2	2	2	1	1	1	1	0	¼	¼	½	¾	1	½	½
Thigh	2	2	2½	3	2½	2½	2	2	1	¾	1	¾	½	½	¼	¼

The patient was put to bed, with a baker over his legs at a temperature of 95° F., boric acid dressings were applied to the ulcer, and the compression-release treatment was given six hours daily. Within eight days the ulcer healed completely. Pain in the foot disappeared after the first day of treatment. On the tenth day, before discharge from the hospital, oscillometric readings were again obtained (Table II.)

It will be observed that there was a remarkable increase in the oscillometric reading. It is of interest to state that the right dorsalis pedis artery could now be palpated.

CASE 2.—D. C., sixty-three years old, Jewish male, was admitted to the hospital Aug. 14, 1935. He gave a one-year history of attacks of very painful intermittent claudication in the calf of the right leg on walking one block, which pain subsided after five minutes' rest. He smoked twenty cigarets a day. The feet were cold, the right foot more than the left. No dorsalis pedis, posterior tibial, or popliteal pulsation was obtained in either leg.

TABLE III A

OSCILLOMETRIC READING—AT 120 MM.

	RIGHT LEG	LEFT LEG
Dorsalis pedis	0	0
Lower ⅓ leg	¼	½
Upper ⅓ leg	½	½

TABLE III B

HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	88.5° F.	90.4° F.	85.0° F.
After 20 minutes' immersion of hands in hot water (110° F.)	91.3° F.	93.0° F.	85.0° F.

These tests indicated the existence of peripheral vascular sclerosis with partial obstruction.

Wassermann test was negative. Blood chemistry, blood count, and urinalysis were all normal. The electrocardiogram showed left axis deviation.

Before admission to the hospital, treatment consisted of rest, infra-red ray therapy, diathermy, and discontinuance of smoking. He had received intravenous hypertonic saline three times a week for two months also. There had been no improvement.

On August 15, the patient was started on venous compression treatment at 30 mm. pressure, alternating two minutes of pressure with two minutes of release for twelve hours a day with no additional form of treatment. The results are presented in the graph (Fig. 1). It will be seen that, beginning with the third day of treatment, there occurred a rapid and marked improvement in the walking ability of the patient. He reached the peak of improvement in seven days and remained at the same level, in spite of further treatment. After one week the patient was able to walk three times the control distance, and it took twice as long for claudication to appear. After three weeks of treatment, the patient stated that he was able to walk fifteen blocks before onset of pain.

It is interesting also to mention that there occurred a rise of 4.1° F. in the temperature of the involved foot after one hour of intermittent compression treatment.

The patient was then discharged for one month. At the end of that time, examination disclosed a return to his original condition. Since resuming daily treatments for two hours, he has again recovered his improved vascular capacity.

CASE 3.—W. H., thirty years old, Jewish male, was admitted June 19, 1935, with the following history: Three years before, the patient noticed a swelling on his right large toe. He consulted a physician, who operated upon him for an ingrown toenail. He remained in bed for eight months following this operation, because of pain in his foot and failure of the wound to heal. One year ago he consulted Dr. Leo Buerger, who made a diagnosis of thrombo-angiitis obliterans. He was treated for twelve weeks with slight improvement but subsequently was confined to bed for eleven months. During the preceding two months, the large toe became

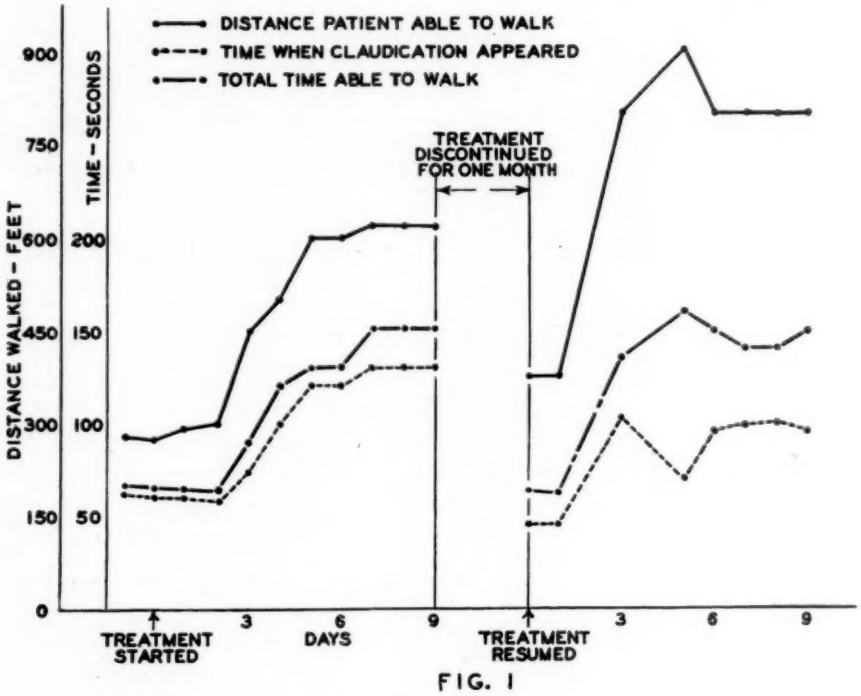

FIG. 1

progressively worse and turned black, with the bone of the distal phalanx exposed. His pain was unbearable, especially at night. He resorted to the use of large doses of codeine and aspirin for relief and, at that time, described his condition as being "only a shell of his former self." He had, up to the time of admission, smoked incessantly, twenty to thirty cigarets per day.

Examination disclosed a well-nourished male, with negative physical findings except in his lower extremities. The right foot was cyanotic and cold, and there existed a gangrenous area involving the distal half of the right great toe, with the bone of the distal phalanx exposed. There was no palpable pulsation of the dorsalis pedis, posterial tibial or popliteal arteries of either leg. The oscillometer showed no pulsations of the right lower extremity up to the lower third of the thigh. The left extremity showed an oscillometric reading of 3.5 at the lower third of the thigh but no oscillations below the knee. There was pallor on elevation and rubor on dependency in both legs, more marked on the right.

TABLE IV

HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	79.1° F.	81.0° F.	75.0° F.
After 35 minutes' immersion of hands in hot water (110° F.)	80.0° F.	83.4° F.	75.4° F.

The admission diagnosis was thrombo-angiitis obliterans, with osteomyelitis of the distal phalanx of the right great toe, which diagnosis was confirmed by x-ray examination. Urinalysis, blood count, blood chemistry, and Wassermann examinations were all negative. He was given the following treatments: bed rest, continuous baking at 95° F., intravenous injections of 250 c.c. of 5 per cent saline every other day, alternating with 2 c.c. of pancreatic extract (insulin-free) intramuscularly every other day, daily foot soak at 95° F. for twenty minutes; smoking was promptly and completely stopped.

Fig. 2.

In spite of all this extensive therapy, the gangrene advanced to involve the entire great toe plus the second and third toe, and two weeks later the entire distal half of the foot was gangrenous (Fig. 2). His pain was intense and required 8 grains of codeine, 40 grains of aspirin and one-half pint of whisky per day for partial relief.

On July 21, one month after admission, all treatments were stopped except the baking, and the intermittent venous compression machine was applied, using 25 mm. of mercury pressure for two minutes alternating with two minutes of release for twelve hours daily. Within twenty-four hours, there was a marked relief of pain. The patient now required only 1 grain of codeine a day for complete relief.

Observations on several successive days showed that the blueness of the foot was fading and that the patient was very comfortable. On the sixth day of treatment, the patient stated that he had had the most comfortable night since his stay in the hospital. After eight days of treatment, several small islands of granulation tissue appeared in the margin of the gangrenous lesion, and the next day

bleeding was observed. Two weeks later the machine was stopped for three days, during which time the patient again complained continuously of very severe pain which was immediately relieved upon the resumption of treatment with the machine.

On August 15, the Landis immersion test produced no rise in temperature with the hands in hot water. The oscillometric reading was one-quarter in the upper third of the right leg at 120 mm. of pressure. Readings distal to this were all zero.

On August 17, it was decided that the patient's period of illness should be shortened by amputating the gangrenous portion of the foot. Although the surgeon expressed the opinion that the point of amputation was indicated at mid-thigh, we prevailed upon him to amputate above the ankle, since all clinical signs pointed to an improved circulation since the introduction of intermittent venous compression. The amputation was performed 2 inches above the maleoli. It was observed at the operation that, on incision through the soft parts, there was considerable ooze, requiring the use of hemostatic clamps. When the anterior and posterior tibial arteries were cut, no bleeding occurred. The arteries were completely occluded by organized thrombi. It was obvious that all this unusual bleeding came from the increased collateral circulation. The toxic temperature immediately subsided, and one week later the patient was discharged from the hospital with the wound healed by primary union.

CASE 4.—J. F., fifty-three years old, Italian male, a porter, first came under observation March 25, 1932, with a history of diabetes of four years' duration. He had been on a diet with insulin for one year. Three months before he had begun to complain of pain in his right foot, coldness, and claudication on walking. One month before, a painful ulcer had appeared on the right large toe which had since refused to heal. Examination disclosed, besides his diabetes, characteristic evidence of severe peripheral vascular sclerosis of both legs, worse in the right. No palpable pulsations were obtained in dorsalis pedis or posterior tibial arteries of either leg. The oscillometric reading was zero in the lower third of the legs. There was an unhealthy appearing ulcer on the medial surface of the terminal portion of the right large toe. He was treated with bed rest, contrast baths, continuous baking, foreign protein, and injections of 300 c.c. of 5 per cent saline intravenously three times a week for six months. The ulcer healed completely in this period. Oscillometric studies on discharge showed traces of oscillations in the lower one-third of his legs. It is interesting that a growth of entirely new toenails occurred, indicating apparent improvement in nutrition of the tissues.

Three years later, the patient appeared with another ulcer on the medial surface of the tip of the right second toe. Examination, this time, disclosed evidence of progressive peripheral sclerosis since the last visit. The ulcer was extremely painful, especially at night, and necessitated the daily use of 4 grains of codeine. The patient was placed on the following regime: 300 c.c. of 5 per cent saline intravenously every other day, continuous baking, bed rest, daily warm baths, and frequent use of wet dressings. At the end of five months the foot was still painful and no healing had occurred—a response vastly different from that in our former experience with him. The results of functional tests made at this time are given in Table V.

TABLE V

HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	81.0° F.	82.4° F.	80.6° F.
After 30 minutes' immersion of hands in hot water (110° F.)	81.4° F.	84.9° F.	80.6° F.

Oscillometry showed no oscillations up to the knee. X-ray films showed calcification of blood vessels in his feet. There was no bleeding from the ulcer.

All previous treatment was stopped, and he was treated with the compression-release machine at 60 mm. of pressure for two hours daily. Within five days the pain had entirely disappeared. The patient stated that he had a sense of warmth in his feet, and he slept without medication. The walking test showed startling improvement in the functional capacity of his vessels (Fig. 3). At the end of two weeks of treatment, the ulcer showed clear evidence of healing. Probing the sinus produced marked bleeding in spite of the fact that oscillometric readings remained 0. The patient was not confined to bed. Three weeks later x-ray films showed an osteomyelitis of the terminal phalanx. Local amputation of the toe was performed and the stump healed in two weeks.

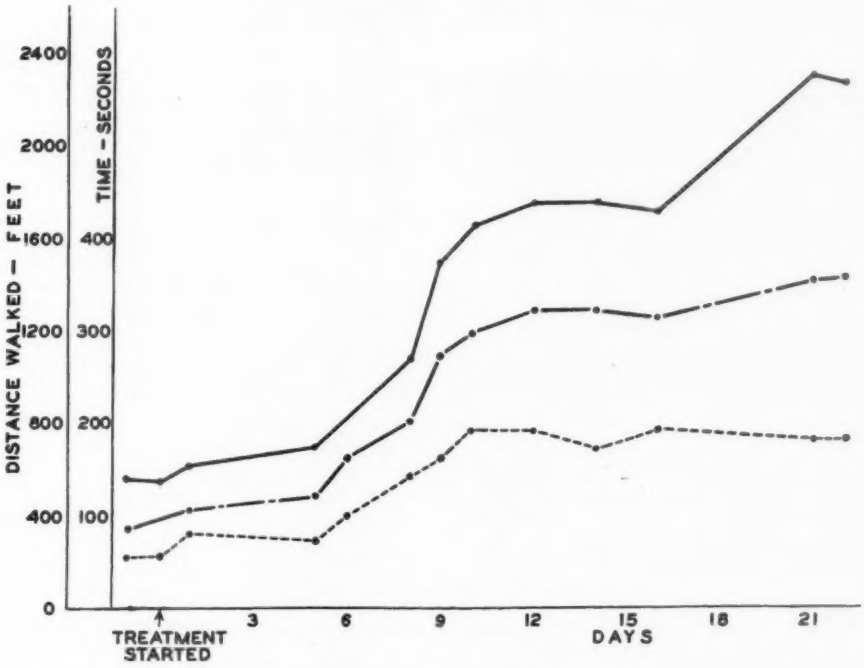

Fig. 3.—●———● Distance patient was able to walk.
● - - - ● Time when claudication appeared.
● —— ● Total time patient was able to walk.

CASE 5.—B. S., a fifty-seven-year-old Jewish male, was admitted to the hospital Sept. 2, 1935, with the following history: He had had a mild form of diabetes for ten years, adequately controlled with slight dietetic restrictions. Since the age of thirty years, he had had difficulty with his lower extremites. For the past ten years, he had had intermittent claudication and complained that his feet were continually cold. Three weeks before admission, he sustained a burn from a hot water bag on the outer surface of his left small toe. It rapidly became infected, and, in four days, this toe became gangrenous. The infection spread to involve the outer distal half of his left foot. He had fever for ten days. Examination disclosed an acutely ill male, temperature 102.6° F. There was a gangrenous ulcer at the base of the left small toe three-quarters of an inch in diameter. The toe itself was black. The dorsal and lateral surfaces of the fourth toe were also gangrenous. The foot was edematous, and lymphangitic streaks extended up to

the middle of the leg. Vascular studies on extremities showed no pulsations obtained in dorsalis pedis, posterior tibial, or popliteal arteries of either leg; oscillometric readings were zero below the knees.

TABLE VI

HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	82.9° F.	82.0° F.	75.0° F.
After 30 minutes' immersion of hands in hot water (110° F.)	86.0° F.	82.8° F.	75.5° F.

The Wassermann test was negative. The blood count showed 23,400 white blood cells, with 84 per cent polymorphonuclear leucocytes. Urine showed traces of

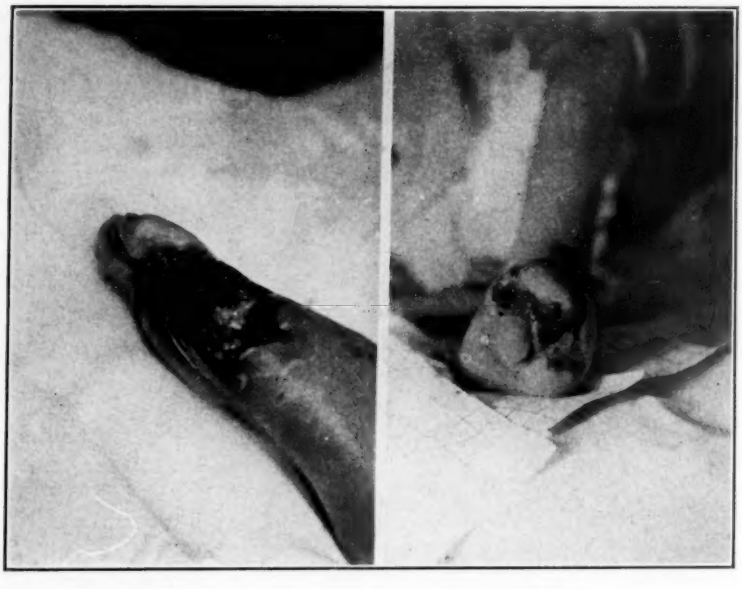

Fig. 4. Fig. 5

sugar, and blood sugar was 131 mg. per cent. The diagnosis was diabetes and peripheral vascular sclerosis with infected gangrene, involving the two lateral toes of the left foot.

For one week, he was treated with wet dressings and baking. The gangrenous lesion continued to spread and to involve the third left toe. His temperature ran a septic course. He complained of a great deal of pain and required the frequent administration of large doses of morphine, codeine, and aspirin. This period was used as a control period.

On the eighth day, venous compression at 60 mm. of mercury and release were started for three hours a day.

Within twenty-four hours, his temperature had subsided, and his pain had almost entirely disappeared. The lesion rapidly became localized. The necrotic slough was removed, and the gangrenous toes were disarticulated without touching the viable tissue. Forty-eight hours after treatment had been started, granulation tissue began to appear on the outer margin of the gangrenous ulcer (Fig.

4). Within a week, the granulation tissue had covered the heads of the exposed metatarsal bones. Within two months all the remaining toes underwent spontaneous amputation and the patient was left with a painless, healthy, granulating stump. At the end of four months of treatment, skin had grown over one-half of the ulcer (Fig. 5).

It is interesting to note that the patient complained of pains and paresthesias in the toes of the uninvolved foot. After two days of compression treatment of this leg, these symptoms promptly disappeared.

CASE 6.—F. S., sixty-four years old, Jewish, a presser by occupation, was admitted on Aug. 30, 1935. He stated that for the five previous months he had had pain in the right calf on walking one block. His feet felt cold. Lower extremities showed the following: feet cold, no dorsalis pedis pulsation obtained in the right foot, but faint pulsations present in the left. X-ray examination showed calcification of blood vessels of both legs and feet. Blood pressure was 162/98.

TABLE VII A

OSCILLOMETRIC READINGS (MAXIMUM AT 140 MM.)

	RIGHT	LEFT
Foot	0	0
Above ankle	0	0
Below knee	0	0
Above knee	½	1

TABLE VII B

HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	81.2° F.	82.1° F.	79.2° F.
After 30 minutes' immersion of hands in hot water (110° F.)	83.9° F.	85.5° F.	79.3° F.

Functional walking test showed that he was able to walk 547 feet at eleven paces per five seconds. Pain occurred in 70 seconds, and he ceased walking in 90 seconds. The diagnosis was peripheral vascular sclerosis with partial obstruction and functional incapacity.

He was treated with alternating venous compression and release at 20 mm. of mercury for one hour three times a week and was then admitted to the hospital, where he was given this treatment twelve hours every day for twelve days. The results are seen in Fig. 6. It will be observed that the patient showed a definite increase in walking ability after twelve days of treatment.

A note of interest is the observation that the skin temperature rose 4.2° F. after one hour of treatment.

TABLE VIII

SKIN TEMPERATURE

	BASE OF RIGHT GREAT TOE	BASE OF RIGHT FOURTH TOE	BASE OF LEFT GREAT TOE	BASE OF LEFT FOURTH TOE
Before treatment	79.2°	79.8°	80.2°	81.5°
After treatment for one hour with alternating venous compression and release	83.0°	83.8°	84.8°	85.6°
Total rise	3.8°	4.0°	4.6°	4.1°

It is interesting, also, that although he had difficulty in walking from the subway to the hospital for treatment, he was able to walk back the same distance with ease after treatment.

CASE 7.—H. G., fifty years old, male, Jewish, was admitted on Sept. 24, 1935, with a history of having trimmed a callus on his right large toe four months before. The toe had become infected, swollen, painful, and had begun to discharge pus. He had treated the toe with local antiseptics and wet dressings. At the end of two months, his physician had discovered that the patient was diabetic. He had immediately been given a diet and 35 units of insulin a day. Despite continuous treatment with baking, wet dressings, and bed rest, his toe became steadily worse, and he was referred to the hospital. On examination he was found to have a sinus tract arising from an ulcer one-half inch in diameter on the medial surface of the right great toe and extending approximately one inch into the deeper structures.

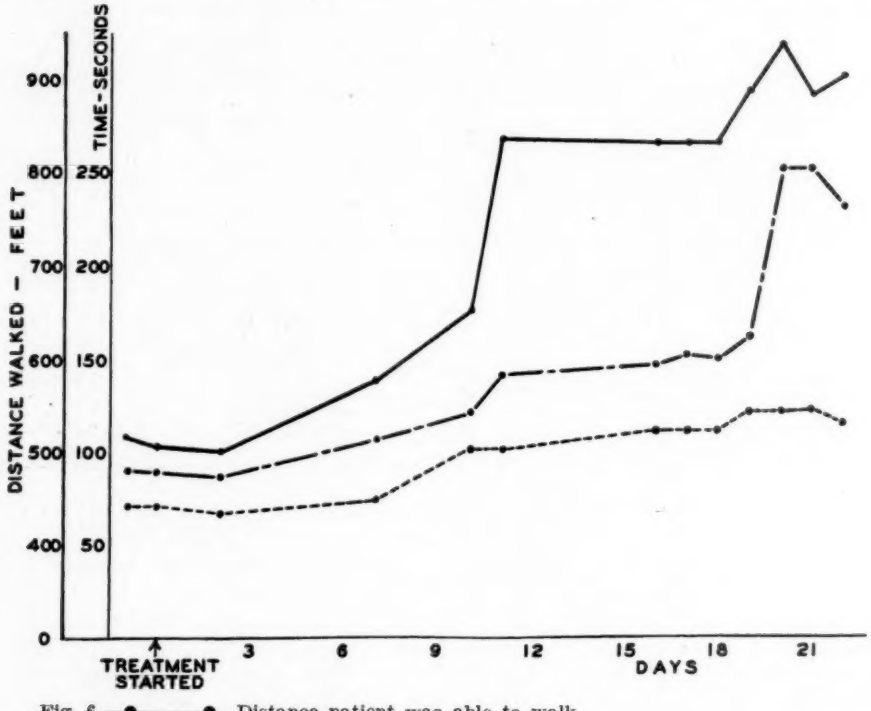

Fig. 6.—●———● Distance patient was able to walk.
●- - -● Time when claudication appeared.
●——● Total time patient was able to walk.

Probing the sinus gave a sensation of grating bone. There was no bleeding. The toe was painful, swollen, red, edematous, and very tender to touch. X-ray examination showed osteomyelitis of the base of the proximal phalanx and marked calcification of the vessels of both feet. Results of the vascular study on admission are given in Table IX, A and B.

TABLE IX A

HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	81.4° F.	83.6° F.	77.6° F.
After 30 minutes' immersion of hands in hot water (110° F.)	84.0° F.	87.6° F.	77.8° F.

TABLE IX B

OSCILLOMETRIC READINGS

	RIGHT LEG								LEFT LEG							
Blood pressure	220	200	180	160	140	120	100	80	220	200	180	160	140	120	100	80
Dorsal pedis	0	0	0	0	0	0	0	0	0	0	0	0	0	Tr	Tr	¼
Lower ⅓ leg	0	0	0	Tr	¼	¼	Tr	Tr	0	0	0	0	¼	¼	¼	¼
Upper ⅓ leg	0	Tr	¼	¼	½	¾	½	½	0	½	¾	¾	1	2½	2¾	2¾
Above knee	4½	3½	3½	3	3	2½	2	2	3½	4½	5	5	4	3½	2½	1½

TABLE X

	RIGHT LEG								LEFT LEG							
Blood pressure	220	200	180	160	140	120	100	80	220	200	180	160	140	120	100	80
Dorsal pedis	0	¼	¼	¼	¼	¼	¼	¼	¼	¼	¼	½	¾	¾	1	¾
Lower ⅓ leg	¼	¼	¼	½	½	½	¾	¾	¼	½	½	1	1½	2	2	2
Upper ⅓ leg	2	2	2½	3	3	3	3	3	1½	2	2½	3½	3½	4	3½	3
Above knee	2½	3½	4½	5	5	5	5	5	1½	2½	3	3½	3½	3	2½	2

The diagnosis was peripheral vascular sclerosis with marked obstruction, osteomyelitis, and diabetes.

Treatment was started with venous compression at 30 mm. of mercury alternating with release, two minutes on and two minutes off, for ten hours daily.

Within twenty-four hours the pain had disappeared. Five days after the onset of treatment, a dorsalis pedis pulse was obtained, and, on probing, profuse bleeding occurred. Oscillometric readings are given in Table X.

There was clear evidence that a marked improvement in vascularity had occurred. It was then decided that the sinus should be exposed and the infected bone curetted. At the operation, bleeding was so profuse that it could be controlled only with hemostatic clamps. The compression treatment was continued after operation. Temperature remained normal. There was no pain. The discharge from the wound was purulent and bloody. At the end of one week, probing disclosed the existence of necrotic bone, which was removed. Two weeks later, a healthy, vascular, granulating wound was present.

CASE 8.—F. C., a sixty-year-old Jewess, was admitted April 26, 1935, with a history of diabetes of twelve years' duration. One year before she had begun to complain of pain and coldness in the right foot, worse on walking. Six weeks ago, an ulcer, which became progressively larger, appeared on the dorsum of the foot. Examination disclosed an aged woman, poorly nourished, with evidence of marked, generalized atherosclerosis. Her blood pressure was 164/90. On the dorsum of the right foot was a large gangrenous area, 2 inches in diameter, sharply demarcated, with surrounding redness. The gangrenous skin was dry and leathery. There were lymphangitic streaks extending to the upper third of the leg. Vascular study showed the following: no dorsalis pedis, posterior tibial, or popliteal pulsation in either leg. Both feet were cold.

TABLE XI A

HOT WATER IMMERSION TEST (LANDIS)

	RIGHT FOOT	LEFT FOOT	ROOM TEMPERATURE
Control	79.2° F.	79.6° F.	76.8° F.
After 30 minutes' immersion of hands in hot water (110° F.)	79.5° F.	79.9° F.	76.8° F.

TABLE XI B

OSCILLOMETRIC READINGS

	RIGHT LEG	LEFT LEG
Foot	0	0
Lower ⅓ leg	0	0
Upper ⅓ leg	0	1.5
Mid-thigh	0.5	3.0

There were obvious signs that the patient was suffering from a severe form of peripheral vascular sclerosis and a gangrenous ulcer, with secondary infection.

She was put to bed; a continuous boric acid dressing was applied to the lesion; and a baker over both legs was maintained at a temperature of 95° F. In four days the evidence of infection had subsided, and the wet dressings were discontinued. Besides exposing the lesion to dry heat, she was given daily intravenous injections of 150 c.c. of hypertonic saline, at first in 3 per cent concentration but later in 5 per cent.

Her diabetes was mild and was easily controlled with a diet consisting of carbohydrate, 175 gm.; protein, 60 gm.; fat, 100 gm.; and with 5 units of insulin t. i. d.

She was treated for two months in this fashion without making any progress. Her pain was continuous, but worse at night, and she required the daily use of from 6 to 10 grains of codeine. The patient decided to return home because of her very slight improvement. Two weeks later she returned to the hospital because her pain was unbearable. Examination disclosed an exacerbation of the infection, with redness and edema surrounding the ulcer. Her temperature was now 103° F. Blood count showed 12,900 white blood cells and 88 per cent polymorphonuclear leucocytes. A boric acid dressing was reapplied, and her legs were placed under a baker. In addition, the intermittent venous compression machine was applied at 60 mm. of mercury for five hours a day. Within twenty-four hours her pain had almost completely subsided. Within three days, the infection was controlled, and the wet dressings were stopped.

After two weeks of treatment, the Landis immersion test showed a rise of 1.7° F. of temperature in the involved foot, and the oscillometer readings showed a faint oscillation in the upper third of the leg. The ulcer was stationary in size, and, on raising the edge of the leathery skin, the margin of the ulcer appeared healthy. The surgeons, however, basing their judgment on past experiences with diabetic patients over sixty years of age who have such advanced form of arterial sclerosis and extensive gangrenous lesions, decided to amputate her leg at mid-thigh. We prevailed upon them at least to attempt an incision in the lower third of the leg and, if sufficient bleeding did not occur, then to proceed to a mid-thigh amputation. The leg incision showed a remarkable flow of blood, and the amputation was completed at that level. The main arterial trunks were completely occluded both by calcification and thrombosis, but blood flowed continuously from the soft tissues. The surgeon stated that he had never seen so much free bleeding in the presence of such severe arterial obstruction. He applied a mild compression bandage and sent the patient back to bed. For forty-eight hours so much bleeding occurred that the surgeon found it necessary to pack the stump three times in this period. Seven days after operation, the patient developed a Welch bacillus infection, from which she died in three days.

SUMMARY

The use of a new device for the clinical application of the phenomenon of reactive hyperemia by alternating venous compression with release is described. It appears, from this preliminary study, to have the following effects in the treatment of organic peripheral vascular obstruction: (1) relief of pain; (2) increase of skin temperature of extremity; (3) increase in walking efficiency; (4) increase in vascularity, permitting amputation at lower levels; and (5) healing of chronic indolent ulcers associated with vascular obstruction.

We wish to thank Dr. Henry Joachim, the chief of the medical service, for his kind cooperation.

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AN APPARATUS FOR THE PRODUCTION OF INTERMITTENT VENOUS COMPRESSION IN THE TREATMENT OF PERIPHERAL VASCULAR DISEASE*

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EVIDENCE has been presented by Lewis and Grant[1] to show that alternating venous occlusion and release result in an increase in circulation to an extremity.

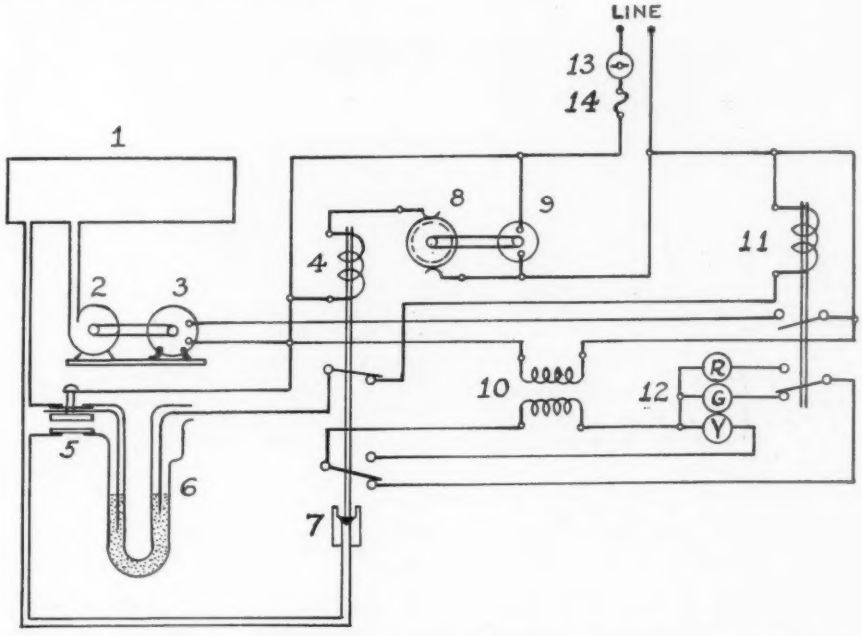

Fig. 1.—Diagram of apparatus: *1*, Pneumatic cuff; *2*, compressor; *3*, motor; *4*, relay; *5*, pressure adjustment; *6*, mercury manometer; *7*, exhaust valve; *8*, timing disk; *9*, synchronous motor; *10*, transformer, *11*, relay; *12*, indicator lights; *13*, switch, and *14*, fuse.

In the preceding article, the authors have given an historical survey of the use of the principle of venous compression and a preliminary report of their experience of its application in seven cases. This article is concerned with a description of the apparatus and its method of application in the treatment of peripheral vascular disease.

The apparatus consists of a motor-driven pump which supplies air to a pneumatic cuff. The pressure of this device is regulated by means of a pressure-measuring indicator. A pressure of 40 mm. of mercury is im-

*From the Metabolic Clinic of the Israel Zion Hospital.

posed on the proximal portion of the diseased extremity and results in a restriction of the returning venous blood. This pressure is applied at a level which does not interfere with arterial filling. It was during the period of compression that Lewis and Grant noticed the development of active arteriolar vasodilation.

A suitable timing mechanism is incorporated in the device which maintains the pressure for two minutes, after which a release valve is actuated electrically to cause an automatic deflation of the cuff. It is during the release period that an increased arterial flow through the extremity occurs. Although Lewis and Grant produced an increase of inflow blood of as great as 600 per cent when venous compression was maintained at 90 mm. of mercury for fifteen minutes, we have found in our experimental observations in the treatment of peripheral vascular

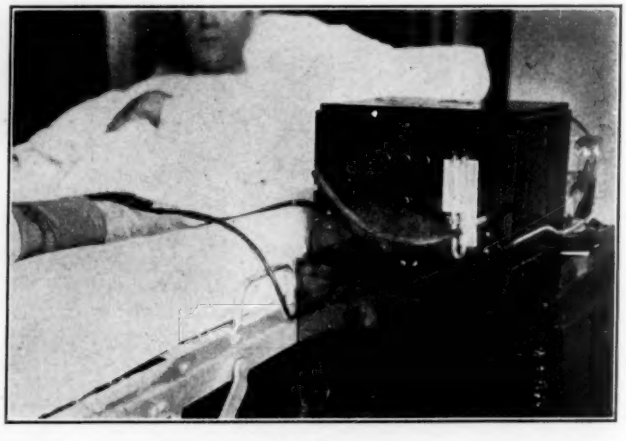

Fig. 2.

disease that a compression of 40 mm. of mercury for two minutes alternating with a similar period of release was much more satisfactory. When, however, no ulcer or gangrene is present and the outstanding symptom is intermittent claudication, pressure up to 90 mm. may be applied. With this routine it has been possible to produce alleviation of pain and increase vascular capacity as determined by functional tests in cases of organic peripheral vascular disease both in gangrenous and nongangrenous cases.

A diagrammatic illustration of the instrument is given in Fig. 1, and the manner of its application is shown in the accompanying photograph (Fig. 2).

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AURICULAR SOUND*

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THE proof that the contraction of the auricles is able to produce an acoustic phenomenon with the characters of a sound, dates from the last century and was determined by simple auscultation (Williams,[1] Stokes,[2] Chauveau[3]) in cases in which the contraction of the auricles was not followed by the corresponding ventricular contraction. Simple listening also permitted the recognition of auricular sound in other conditions, but its genesis and effects could not be recognized until the graphic records of the heart sounds simultaneously with that of other manifestations of the heart's activity, such as electrocardiogram or phlebogram, came into use.

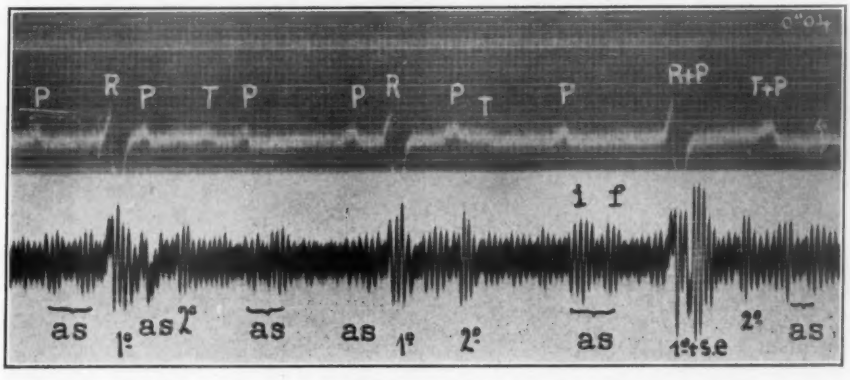

Fig. 1.—Graphic record of the auricular sound (*as*) in a case of complete heart-block; *i*, initial part; *f*, final part; *1° + s.e.* summation of the sound produced at the beginning of ventricular systole with the auricular sound.

The object of the present paper is merely to show synthetically and in a somewhat schematic way, some of the verified acquisitions of knowledge concerning the auricular sound obtained from the graphic record of the heart sounds. The knowledge of those facts and of their detection by the graphic method teaches the examiner to recognize these phenomena merely by listening at the precordium. The reader who desires further details concerning the auricular sound can find sufficient information in the references.

DEFINITION AND GENESIS

We must understand as the auricular sound the acoustic phenomenon produced by the contraction of the auricles, whether this be the result

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of sinus activity (Fig. 1) or of the condition called auricular flutter (Fig. 2). The graphic record of the heart sounds obtained over the precordium (Lewis,[4] Selenin and Fogelson,[5] Cossio,[6] Cossio and Braun Menendez[7]) or through a detector introduced into the esophagus (Benjamin,[8] Braun Menendez and Taquini[9]) shows that the auricular sound is formed by two groups of small oscillations, the second appearing a few hundredths of a second after the first (Fig. 1). As each group of oscillations corresponds to a different sound, we must regard the auricular sound as really formed by two different sounds which are perceived as one only because of the deficiency of the human ear as an acoustic receptor.

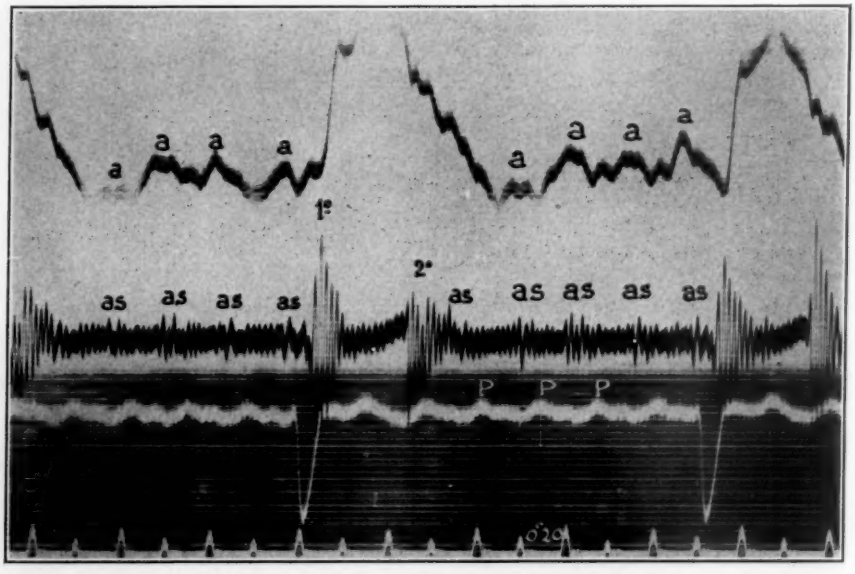

Fig. 2.—Graphic record of auricular sound (*as*) in a case of auricular flutter with complete heart-block. Above, optical record of venous pulse.

The verification that the first group of oscillations of the auricular sound (Cossio and Braun Menendez[7]) is produced during the height of the auricular systole, i.e., when the tension of the auricular walls and the compression of the blood they contain are maximum, shows that the first part or initial portion of the auricular sound is due equally to the vibrations of the auricular walls set in tension and to the vibration of the mass of blood they include and compress, as had been previously hinted by Lewis.[4] The proof that the second group of oscillations of the auricular sound occurs once the auricular systole is finished has induced the idea that the second or final part is due to the vibrations that appear as a consequence of the auricular systole—tension of the ventricular walls produced by the blood expelled into them by the auricular systole

or vibration of the auriculoventricular valves. Because of those two anatomical factors, the auriculoventricular valve is the one more fit to vibrate and generate a sound (Dock[10]), it is natural to attribute the second part of this sound to the tension of this valve and not to the vibration of the ventricular myocardium (Lewis[4] and Cossio and Lascalea[11]). In support of this view is the fact that the second part of the auricular sound is produced at the moment the auriculoventricular valve is higher and, therefore, when its tension is greatest. The different origin of the initial and the final parts of the auricular sound explains the dis-

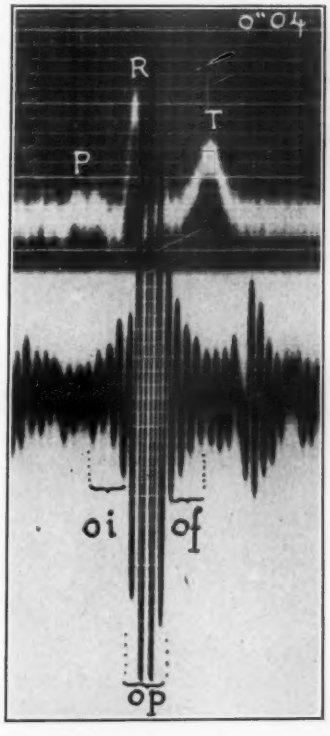

Fig. 3.—Graphic record of first heart sound in normal conditions; *oi*, initial oscillations; *op*, principal oscillations; *of*, final oscillations.

crepancy between its features when detected through the esophagus and over the precordium. When the auricular sound is elicited through the esophagus, it is its initial portion that is more constant and predominates in the record. This is due to the fact that this initial portion is generated, as we have stated, in the walls of the aurieles, and these are situated in intimate contact with the esophagus. On the contrary, when the auricular sound is elicited over the precordium, it is the second part of the sound that predominates because of its origin in the ventricles in close contact with the thoracic wall.

THE AURICULAR SOUND IN NORMAL CONDITIONS

The graphic record of the heart sounds obtained simultaneously with the electrocardiogram or the phlebogram, especially the former, has shown that normally the auricular sound as detected over the precordium is one of the normal constituents of the first heart sound (Cossio and Lascalea[11]) or it presents itself as an independent sound (Bridgman,[12] Wolferth and Margolies,[13] Braun Menendez and Orias[14]), producing the condition called physiological reduplication or splitting of the first heart sound (Cossio,[6] Cossio and Braun Menendez[15]).

Auricular Sound and First Heart Sound.—In normal conditions each auricular contraction is followed almost immediately by its corresponding ventricular contraction. This accounts for the fact that the second part of the auricular sound is produced just before the sound generated

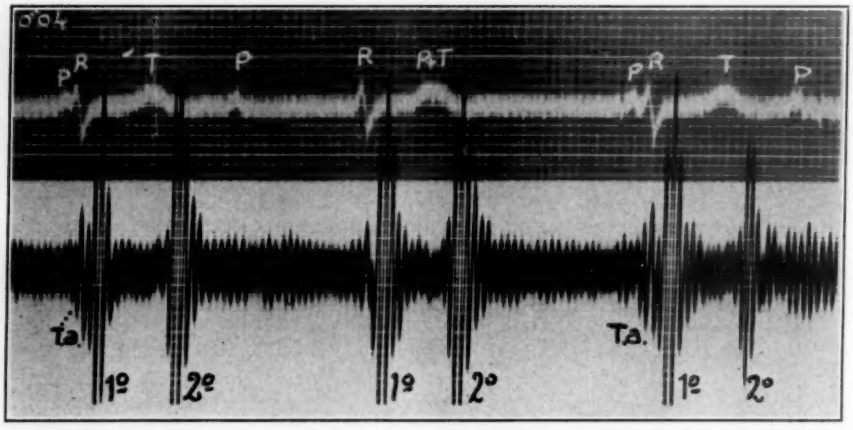

Fig. 4.—Graphic record of the first heart sound with and without the corresponding precedent auricular contraction. The first heart sound has initial oscillations only when the contraction of the ventricles is accidentally preceded by the contraction of the auricles, showing that the initial oscillations of the first heart sound are due to nothing but the auricular sound.

by the auriculoventricular valve when it is put into tension at the beginning of the ventricular systole. The lack of demarcation between those two acoustic phenomena, namely, the final portion of the auricular sound and the initial portion of the sound due to the ventricular systole, causes both to form the single sound called "first heart sound" (Figs. 3 and 4). In other words, the acoustic phenomenon called the "first heart sound" is formed by the succession of two acoustic phenomena produced so closely one to another that they are perceived as one sound.

Auricular Sound and Physiological Reduplication or Split First Heart Sound.—The better transmission of the auricular sound from its place of origin to the precordium, as takes place frequently in childhood (Bridgman[12]), causes it to be perceived as an individual sound, independent of the sound produced by the closure of auriculoventricular

valves. The greater original intensity of the auricular sound, as a consequence of a more lively contraction of the auricles, as happens in the case of overactivity of the heart (emotion or muscular exercise) or at

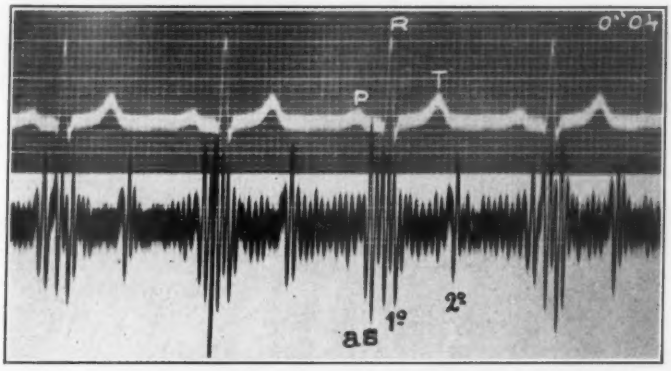

Fig. 5.—Constant reduplication of first heart sound in a healthy person. The auricular sound (*as*) of unusual size appears as an independent acoustic phenomenon, without any relationship to the sound produced at the start of the ventricular systole. That the oscillations *as* are nothing else than the auricular sound is established because it precedes the QRS complex of the electrocardiogram obtained simultaneously.

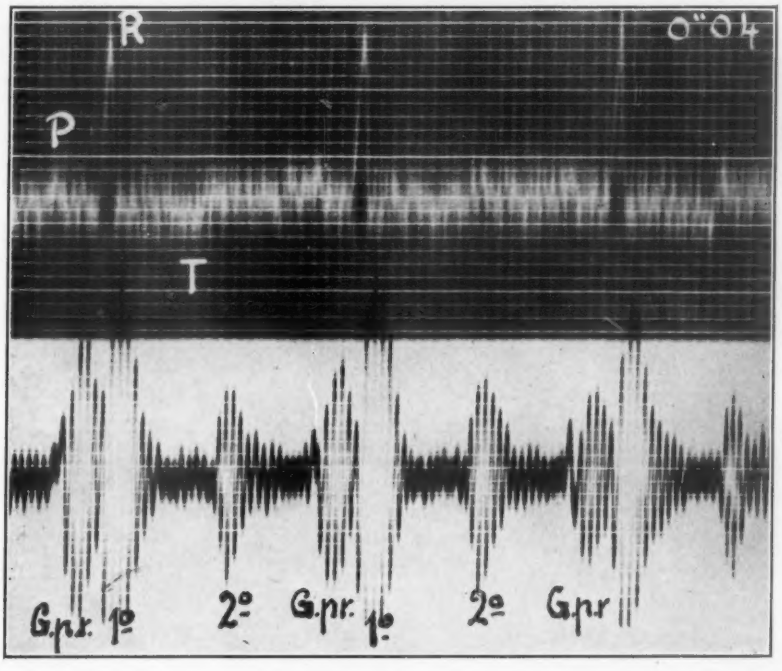

Fig. 6.—Reduplication of first heart sound with a certain cadence of presystolic gallop rhythm in a case of arterial hypertension without heart failure. The sound marked with the letters *G. pr.* precedes the QRS complex and represents an auricular sound of unusual degree.

the end of the expiration (Cossio and Braun Menendez[15]) causes also the auricular sound in the precordium to appear as an individual, isolated sound, independent of the one due to the ventricular systole.

The existence of an auricular sound as an individual acoustic phenomenon independent of the sound that appears at the beginning of the ventricular systole causes the presence of two successive sounds: one produced in the auricles and the other in the ventricles, in place of the normal single sound called "first heart sound." This results in the condition known as reduplicated or split first heart sound, according to the degree of separation of the two successive sounds (Fig. 5).

THE AURICULAR SOUND IN ABNORMAL CONDITIONS

The auricular sound appears over the precordium as an isolated acoustic phenomenon in many abnormal conditions. These conditions

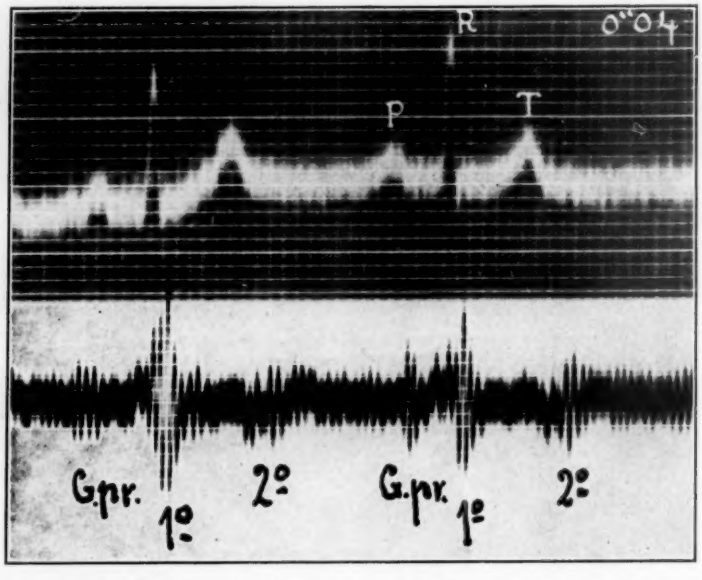

Fig. 7.—Presystolic gallop rhythm produced by the auricular sound (*G. pr.*) independent of the sound produced at the beginning of the ventricular systole. The independence of the auricular sound is due to the increase of the time of the auricular ventricular conduction (P-R = 0.22).

must be considered under two different circumstances. First, when each auricular systole is followed by its respective ventricular systole (sinus rhythm) and, second, when the contraction of the auricles becomes independent of that of the ventricles (complete heart-block).

Sinus Rhythm.—The auricular sound exists as an independent phenomenon without relation to the sound produced at the beginning of the ventricular systole, though each auricular contraction is followed by its corresponding ventricular contraction, in the following conditions: (a) increased energy in the auricular contraction; (b) delay in the conduction of the stimulus from auricles to ventricles; and (c) delayed appearance of the sound produced at the onset of ventricular systole.

When the greater energy of the auricular systole causes a more intense auricular sound, it appears as an isolated phenomenon, independent of the sound produced at the beginning of the ventricular systole. The position of this auricular sound in relation to the initial ventricular sound, and influenced by the heart rate, determines whether it is spoken of as reduplication of the first heart sound or as a presystolic gallop rhythm. Both conditions are found in arterial hypertension (Routier and Van Bogaert,[16] Cossio[6]), in mitral stenosis (Lewis[17]), and in aortic

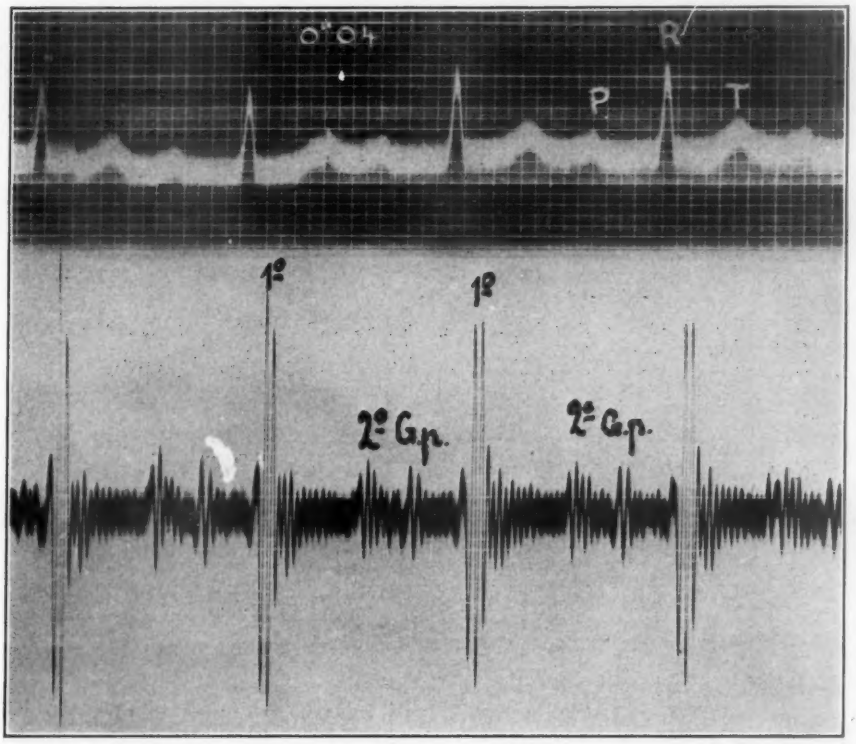

Fig. 8.—Graphic record obtained of the same patient as Fig. 7 but with greater delay of auricular ventricular conduction (P-R = 0.26). Now the auricular sound is situated at the beginning of diastole (*G. p.*).

insufficiency (Laubry and Pezzi[18])—states in which for various reasons the auricular contraction is more lively and generates a stronger auricular sound (Fig. 6).

A moderate delay of the auriculoventricular conduction means an increased interval between auricular and ventricular systole. The final portion of the auricular sound, which in normal conditions forms part of the first heart sound, separates itself from the other component of the first sound, which is produced at the start of the ventricular systole. In this case there are two successive sounds, i.e., the condition called

reduplicated first heart sound or presystolic gallop rhythm, according to the cadence; and those two sounds are due to a disturbance of the auriculoventricular conduction (White,[19] Cossio[6]). If this delay in the conduction is conspicuous, the auricular sound instead of being situated

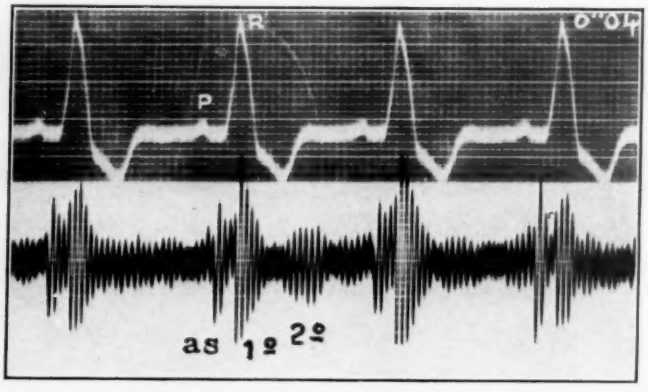

Fig. 9.—Permanent reduplication of first heart sound in a patient with bundle-branch block. In this case the reduplication is due to the independence of the auricular sound (*as*) caused by the delay of the sound produced at the beginning of the ventricular systole (*1°*) as a consequence of the disorder in intraventricular conduction.

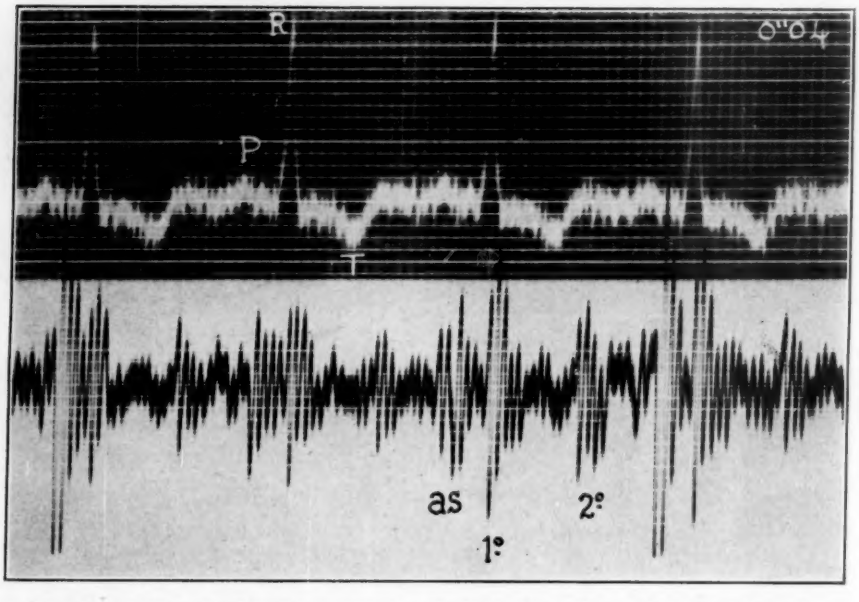

Fig. 10.—Gallop rhythm in a case of arterial hypertension with congestive heart failure. Note the delay in the appearance of the sound that occurs at the beginning of ventricular systole (*1°*) and the anticipation of the auricular sound (*as*) as may be shown by the electrocardiogram, simultaneously obtained.

at the end of the diastolic pause (presystolic gallop rhythm) will be found at its beginning (protodiastolic gallop rhythm) (Laubry and Pezzi,[18] White,[19] Cossio[6]) (Figs. 7 and 8).

The delayed appearance of the sound that is produced at the beginning of the ventricular systole, which is due not to delayed auriculo-ventricular conduction but to a disturbance in the intraventricular conduction, or is caused by a deficiency of the ventricular muscle, produces the separation of the auricular sound from the sound that appears at the initiation of the ventricular systole. This separation also results in the appearance of two successive sounds instead of a single first heart sound (Figs. 9 and 10).

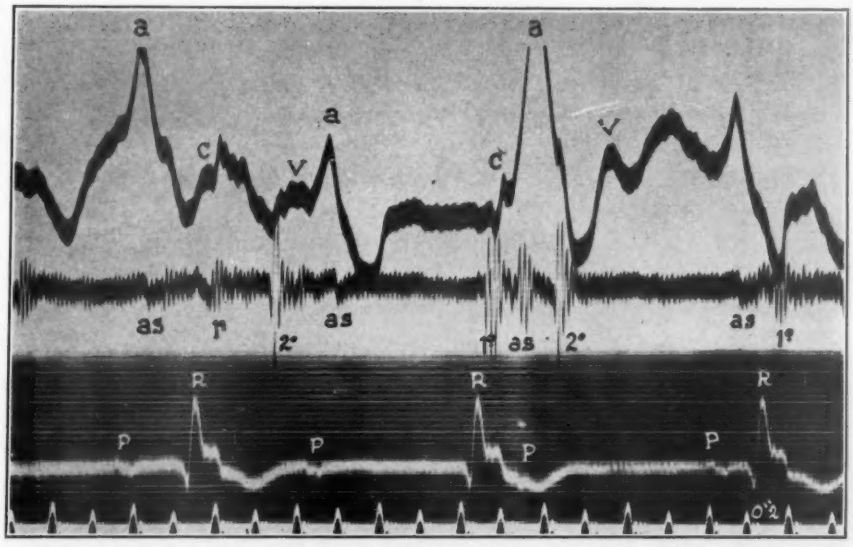

Fig. 11.—Venous pulse, electrocardiogram, and graphic record of the heart sounds in a case of complete heart-block. Note the increased intensity of the auricular sound (*as*) when the contraction of the auricles occurs during the ventricular systole.

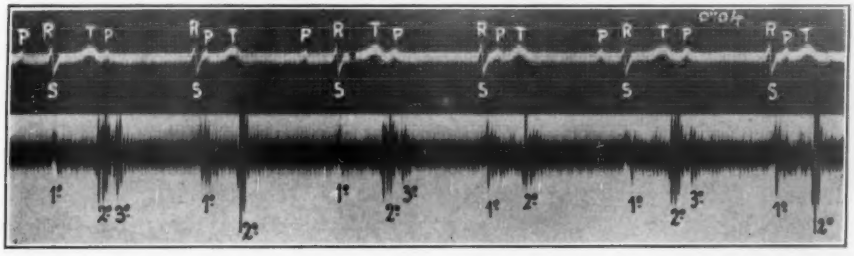

Fig. 12.—Electrocardiogram and graphic record of the heart sounds in a case of complete heart-block. Note the appearance of a third sound (3°) just after the second heart sound (2°), whenever the contraction of the auricles occurs after the ventricular contraction has come to an end, i.e., in the period of rapid filling.

The presence of these two successive sounds, the first auricular and the second ventricular, is known by the name of reduplication of the first heart sound or of presystolic gallop rhythm, according to the cadence. They occur in intraventricular heart-block, especially in the so-called bundle-branch block (Lewis,[20] Cossio[6]) and in heart failure

(Routier and Van Bogaert,[21] Duchosal[22]). In the latter condition it generally assumes the cadence of presystolic gallop rhythm on account of the coexistence of tachycardia and of the conspicuous separation between the auricular sound and the sound that exists at the beginning of ventricular systole. This conspicuous separation between both sounds is due to the fact that, besides the delay of the sound that appears at the beginning of the ventricular systole, there is an anticipation of the auricular sound in relation to the contraction of the auricles (Duchosal[23]).

Complete Heart-Block.—The isolated contraction of the auricles in complete heart-block, i.e., when auricular contraction is not followed by the contraction of the ventricles, causes the auricular sound to appear as an individual phenomenon at the precordium. The complete independence of auricular and ventricular contraction in complete heart-block causes the auricular sound to appear at different moments during the heart's cycle, coinciding occasionally with the sound that is produced at the start of ventricular systole and also now and then with the period of ventricular rapid filling (Figs. 11 and 12). When the auricular sound appears during the great silence of diastole, we have to deal with a very muffled sound, at the extreme limit of audibility. When it appears in the short systolic silence, it is stronger (Cossio and Braun Menendez[7]) and may simulate a reduplication of the first or the second heart sound, according to its position. When the auricular sound coincides by chance with the sound that appears at the beginning of the ventricular systole, both acoustic phenomena are added, and in this case the first sound acquires unusual intensity and may be compared to a cannon shot (Strazhesko[24]). When the auricular sound coincides occasionally with the period of rapid filling, which directly follows ventricular contraction, both effects are added, and there appears a third sound after the second sound of that heart cycle (Cossio and Lascalea[25]).

SUMMARY

1. The auricular contraction produces a sound called auricular sound. The first part of that sound appears at the height of the auricular systole and is more evident at the esophagus. The second part of this sound occurs once the auricular systole is ended and is more evident at the precordium.

2. Under normal conditions the auricular sound is a part of the first heart sound but may appear as an independent sound, being the cause of most of the cases of reduplication of the first heart sound heard in healthy subjects.

3. In a series of abnormal conditions such as arterial hypertension, aortic incompetence, mitral stenosis, delay in the auriculoventricular conduction, and marked intraventricular block (the so-called bundle-branch block), the auricular sound may appear isolated, being the cause

of the acoustic phenomenon called reduplicated first sound and presystolic gallop rhythm that may be present under those circumstances.

4. In complete heart-block the auricular sound is also independent of ventricular systole and may appear during the great diastolic silence or the shorter systolic silence, simulating in this case a reduplication of the first or the second heart sound. It may likewise coincide and strengthen occasionally the first heart sound, or, if coinciding with the period of rapid filling of a heart cycle, cause the presence of a third heart sound following the second sound.

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ELECTROCARDIOGRAPHIC CHANGES FOLLOWING CORONARY SINUS OCCLUSION IN THE DOG'S HEART*†

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BASED upon observations made by Gross[1] on the available mechanisms by which the human heart attempts to compensate for occlusion of the coronary arteries or their branches, Gross and Blum[2, 3, 4] produced obturation of the coronary sinus in the dog's heart in order to increase the vascular bed. They were able to show that, following coronary sinus obturation, ligation of the left anterior descending coronary branch either completely prevented the formation of an infarct, which otherwise almost invariably follows this procedure, or diminished its size considerably. The present report deals with the electrocardiographic findings in a series of 66 dogs on which partial or complete obturation of the mouth of the coronary sinus was produced.

Very few reports have been published on the effects of coronary sinus obturation. Cohnheim and von Schultess-Rechberg (1881)[5] observed enormous stasis in the dog's myocardium following coronary sinus occlusion. Robertson[6] observed bulging of the coronary sinus and veins, cyanosis of the left heart, petechial spots, slowing of the heart rate, and

TABLE I

METHODS EMPLOYED TO PRODUCE CORONARY SINUS OBTURATION AND DEGREE OF OCCLUSION OBTAINED

PROCEDURE	NO. OF DOGS	DEGREE OF OCCLUSION		
		COMPLETE	PARTIAL	UNSUCCESSFUL
I. Ligature alone	24	11	7	6
II. Ligature and dissection	5	5	0	0
III. Ligature and escharotics* (perisinus and intrasinus)	12	5	4	3
IV. Perisinus injection of escharotics	15	0	13	2
V. Intrasinus injection of escharotics by use of transauricular cannula	8	2	2	4
VI. Intrasinus injection of escharotics with temporary ligature†	2	2	0	0
Total	66	25	26	15

*Escharotics used were: 5 per cent and 10 per cent sodium morrhuate; 30 per cent sodium salicylate; tincture of green soap (1 to 2 c.c. were injected).

†Ligature around mouth of coronary sinus held in place from 5 to 10 minutes—then removed.

*From the Laboratories of The Mount Sinai Hospital.

†Aided by a grant from the Lucius N. Littauer and the Walter W. Naumburg Funds.

decreased contractility following such occlusion. The only report on electrocardiographic findings following coronary sinus occlusion is that by Otto.[7] Although he also produced vagus nerve section in all of his twelve dogs, and section of the accelerator nerve in seven of them, he did not believe that this influenced the effects which he observed following coronary sinus ligation. Following this procedure, there occurred engorgement of the large veins, cyanosis, and functionless involvement of the left ventricle, incomplete heart-block and maintenance of the regular rhythm by the auricles. Ten of his twelve dogs died within an

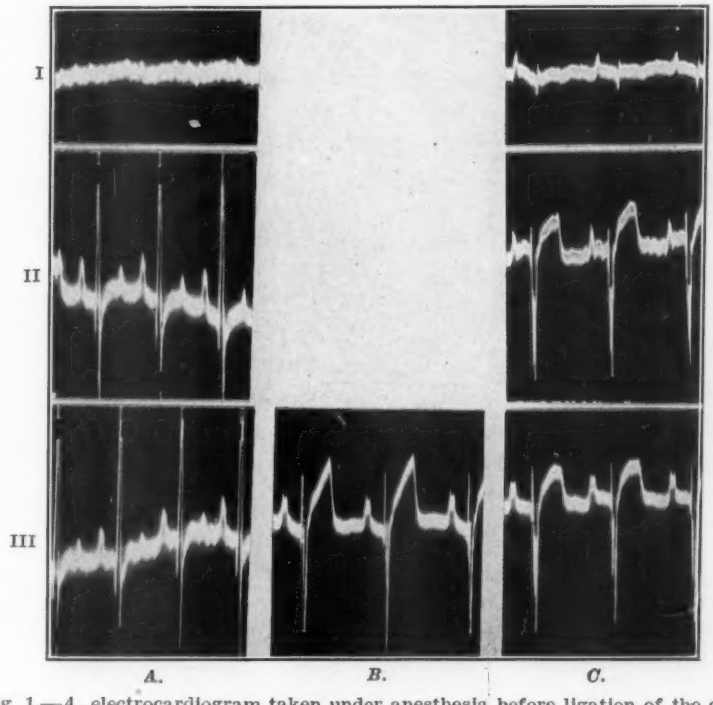

Fig. 1.—*A*, electrocardiogram taken under anesthesia before ligation of the coronary sinus. Note low voltage in Lead I.

B, Lead III taken seven minutes postoperatively. Note slowing of the heart, notching and downward direction of the QRS main deflection, and elevation of the R-T transition.

C, electrocardiogram taken twenty minutes postoperatively. Note the slowing of the heart, notching and downward direction of the QRS main deflection, and elevation of the R-T transition in Leads II and III.

hour following the coronary sinus occlusion. Electrocardiographic tracings (Lead II) showed constant elevation of the T-wave. In two instances R-T fusion appeared.

In the studies presently reported (incorporated in a preliminary report[8]), ligation and injection of escharotics (sodium morrhuate, sodium salicylate, and tincture of green soap) into and around the coronary sinus was employed to produce coronary sinus occlusion in sixty-six

dogs. All procedures were carried out as close to the coronary sinus mouth as possible. Complete, partial and unsuccessful obturations were obtained. Table I shows the methods employed and the degree of obturation obtained as determined at autopsy.

Electrocardiographic tracings were taken before, during, and at various intervals of time after the coronary sinus procedures. Because of the fact that low voltage frequently occurs in Lead I of dogs (Fig. 1), changes in this lead were difficult to evaluate and therefore were eliminated. The consistent electrocardiographic changes observed in the several groups of experiments were as follows: (1) elevation of the R-T transition; (2) notching and downward direction of the main QRS deflection; (3) inversion of the T-wave; and (4) temporary slowing of the heart rate.

Large T-waves of a transitory nature were occasionally noted. These were observed after the first week and occurred with equal frequency in the several groups of procedures listed. Partial heart-block was noted in two dogs in which the coronary sinus was completely ligated. Both of these dogs died within twenty-four hours after the operation.

Slowing of the heart rate was observed immediately following coronary sinus ligation. This occurred almost invariably. The slowing lasted a few minutes and did not take place when escharotics alone were used for the obturation. This was probably due to the fact that escharotics do not produce a sudden and complete obturation. It also indicates that the slowing of the heart rate following obturation is not due to irritation at the mouth of the coronary sinus.

Complete ligation of the coronary sinus produced a dilatation of the entire heart. The superficial veins became engorged and the left ven-

TABLE II

ELECTROCARDIOGRAPHIC FINDINGS FOLLOWING COMPLETE OBTURATION OF CORONARY SINUS

PROCEDURE	DOGS WITH RECORDS IMMED. TO 24 HR.	DOGS WITH RECORDS 1 DAY TO 4 WK.	QRS		R-T	T
			DOWN	NOTCHED	ELEVATION	INVERSION
I. Ligature alone	4	8	4 1	3 1	4 4	0 2
II. Ligature and dissection	4	5	0 0	2 1	4 5	4 4
III. Ligature and escharotics (perisinus and intrasinus)	3	3	3 0	1 1	3 1	0 0
V. Intrasinus injection of escharotics by use of transauricular cannula	2	1	0 0	1 1	0* 0	0 0
VI. Intrasinus injection of escharotics with temporary ligature	2	1	0 0	0 0	1 0	1 0

*Temporary elevation of R-T while cannula was in place.

tricle became cyanotic up to and slightly beyond the interventricular grooves. Occasionally ecchymotic spots appeared on the surface of the left ventricle. The right ventricle retained its normal color except for a strip adjacent to the interventricular grooves, particularly on the posterior aspect of the heart.

Table II summarizes the electrocardiographic findings following complete obturation at the mouth of the coronary sinus.

As will be noted, all records taken immediately after complete ligation of the coronary sinus mouth, without dissection, showed a downward direction of the main deflection of the QRS and an elevation in the R-T transition (Fig. 2). Three of the four animals showed notching of

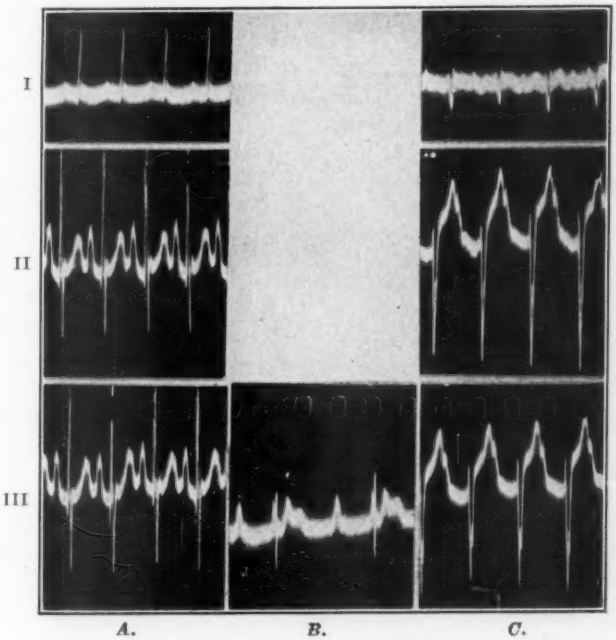

Fig. 2.—*A*, electrocardiogram taken under anesthesia before ligation of the coronary sinus.

B, Lead III taken fifteen minutes postoperatively showing 2 to 1 heart-block.

C, electrocardiogram taken thirty minutes postoperatively. Note the notching and downward direction of the QRS main deflection in all leads, and the elevation of the R-T transition in Leads II and III.

the QRS. When the coronary sinus was dissected before ligation, immediate records showed no downward direction of the QRS deflection; notching of the QRS was less frequent; the T-waves were inverted in all four cases; and the R-T transition was elevated (Fig. 3).

The combined procedure in which ligation and injection of escharotics either into or around the coronary sinus produced complete obturation, gave electrocardiographic results similar to those mentioned above; all cases showed elevation of the R-T transition and downward direction of the QRS deflection.

When complete obturation was obtained by thrombosis following injection of an escharotic into the lumen of the coronary sinus at its mouth, the electrocardiographic changes were inconstant. In one case (Table II) after the cannula was placed in the coronary sinus and the escharotic was introduced, the electrocardiogram showed an elevation of the R-T transition. After the cannula was removed the R-T elevation disappeared. This suggests that the R-T elevation may be related to the sudden increase in venous blood within the myocardium (anoxemia?).

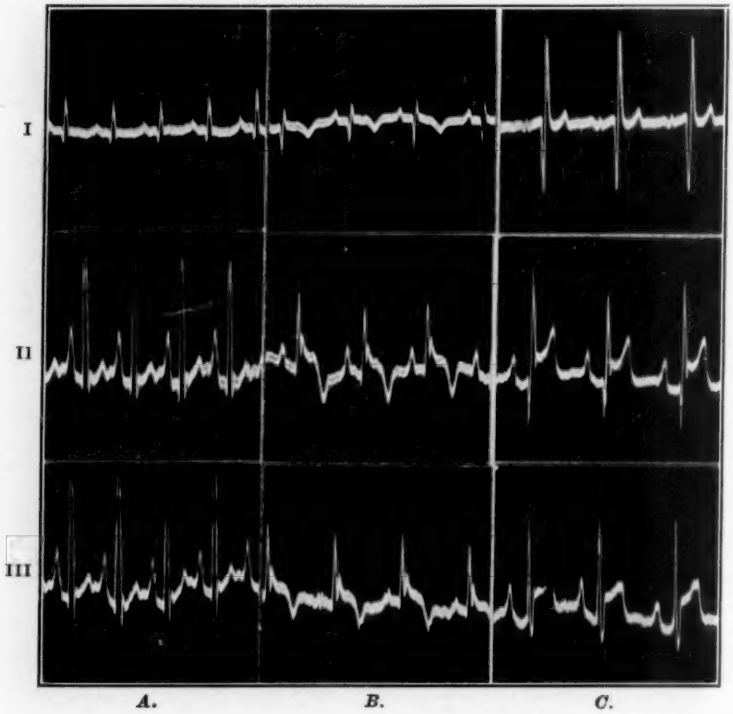

Fig. 3.—*A*, electrocardiogram taken under anesthesia before dissection and ligation of the coronary sinus.

B, electrocardiogram taken sixteen hours postoperatively. Note lower voltage, notching and slurring of the QRS, the elevation of the R-T transition in Leads II and III, and the deeply inverted T-waves in all leads.

C, electrocardiogram taken six days postoperatively. Note the persistence of the R-T transition elevation in Leads II and III and the return of the T-waves to the upright position.

All electrocardiographic changes tended to return to normal within from two to four weeks after obturation of the coronary sinus. The inconstancy of the electrocardiographic changes found in Groups V and VI where escharotics alone were used is probably due to the fact that occlusion was not immediate.

Partial occlusion of the coronary sinus was obtained in twenty-six dogs. Table III shows the procedures employed and the results obtained.

TABLE III

ELECTROCARDIOGRAPHIC FINDINGS FOLLOWING PARTIAL OBTURATION OF CORONARY SINUS

PROCEDURE	DOGS WITH RECORDS IMMED. TO 1 DAY	DOGS WITH RECORDS 1 DAY TO 1 WK.	QRS		R-T	T
			DOWN	NOTCHED	ELEVATION	INVERSION
I. Ligature alone	2	7	1 2	2 3	2 3	1 1
III. Ligature and escharotics (perisinus and intrasinus)	3	3	1 0	1 0	2 0	1 1
IV. Perisinus injection of escharotics	11	10	0 0	0 2	7 7	7 3
V. Intrasinus injection of escharotics by use of transauricular cannula	2	1	0 0	1 1	1 1	0 0

As will be observed, both dogs in which ligation alone was performed showed immediate elevation of the R-T transition and notching of the QRS, one with an inverted T-wave and one with a downward direction of the QRS deflection. These changes occurred in spite of the fact that occlusion was only partial. The inconstancy of the other findings noted in Table III may be due to the differences in degree, time, and rate in which the partial occlusion, with its resulting venous stasis, occurred.

TABLE IV

ELECTROCARDIOGRAPHIC FINDINGS FOLLOWING UNSUCCESSFUL OBTURATION OF CORONARY SINUS

PROCEDURE	DOGS WITH RECORDS IMMED. TO 1 DAY	DOGS WITH RECORDS 1 DAY TO 1 WK.	QRS		R-T	T
			DOWN	NOTCHED	ELEVATION	INVERSION
I. Ligature alone	2	6	0 0	0 0	0 0	0 0
III. Ligature and escharotics (perisinus and intrasinus)	1	3	0 0	0 1	0 1	0 0
IV. Perisinus injection of escharotics	1	1	0 0	0 1	0 1	0 0
V. Intrasinus injection of escharotics by use of transauricular cannula	4	2	2 1	3 1	3 1	1 0

Table IV shows the findings in fifteen dogs in which the several procedures listed failed to produce any narrowing of the mouth of the coronary sinus as determined at autopsy. The findings are of interest inasmuch as they form a control group to determine the effect of the several procedures alone without any appreciable coronary sinus occlusion and its effects on venous stasis within the myocardium. It will be

observed that, when a ligature was placed around the coronary sinus and no injection of escharotics was employed, the electrocardiographic findings were completely negative. On the other hand, when escharotics were also used, electrocardiographic changes were sometimes present. In this latter group, it is quite possible that the injection of an escharotic may have produced some degree of obturation (mechanically, by infiltration) which, however, had completely disappeared when the dogs came to autopsy.

It is clear from the above described findings that when ligation alone was employed and occlusion was complete, electrocardiographic changes occurred in all instances; when ligation alone was employed and the lumen of the coronary sinus was not narrowed due to the fact that either accidentally or deliberately the ligature was not tied around the coronary sinus mouth, no electrocardiographic changes followed. Between these two clear-cut groups there are a number of instances in which at some time during the course of the experiment, and not immediately after the experimental procedure, partial or complete occlusion of the coronary sinus mouth was produced. In these groups the electrocardiographic findings were inconstant, but when present were of the nature of those described above.

SUMMARY AND CONCLUSIONS

Partial and complete obturation of the mouth of the coronary sinus was produced in forty-one dogs by means of a variety of procedures including ligation and the injection of escharotics into the coronary sinus lumen or around the coronary sinus. These procedures were employed alone or in combinations. In fifteen additional dogs these procedures were employed without producing appreciable coronary sinus obturation, as determined at autopsy.

Following complete obturation, there occurred dilatation of the heart, engorgement of the superficial veins, and cyanosis of the left ventricle up to and slightly beyond the interventricular grooves. Occasionally small ecchymoses were also observed. The electrocardiographic findings resulting from complete or partial occlusion were notching and downward direction of the main QRS deflection, elevation of the R-T transition, occasional inversion of the T-waves, and temporary slowing of the heart rate. These findings were most constant when occlusion was complete and sudden. It may be of interest to note that the inversion of the T-wave occurred almost invariably if the complete obturation was preceded by dissection of the coronary sinus. This brings up the question as to what rôle this additional injury may have played in the production of the electrocardiographic changes. On the other hand, the marked RST changes occurred whether or not there was local injury to the heart. These were, therefore, probably associated with congestion of the heart.

A contributing factor in causing inversion of the QRS deflection may have been the change in position or rotation of the heart produced by the congestion which occurred mainly in the left chambers.

No changes were found following the insertion of the ligature around the coronary sinus without occlusion. Partial obturation produced electrocardiographic findings similar to complete occlusion, but the changes were less constant in their occurrence. All electrocardiographic changes tended to disappear within a period of from two to four weeks after the occlusion was produced.

The RST changes, when present, were similar to those observed following acute coronary occlusion, but unlike the latter they did not present the pathognomonic steady progression into inverted T-waves. Thus, following coronary sinus occlusion, the heart gradually readjusts itself, and the electrocardiographic tracings return to normal.

It is suggested that the electrocardiographic findings reported may result from a temporary injury of the myocardium due to oxygen insufficiency attendant on venous congestion. Other factors, such as local injury due to manipulation, and change in the position of the heart, probably play minor rôles.

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DIGITALIS EOSINOPHILIA*

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RECENT observation of a patient who manifested an eosinophilia, seemingly in response to digitalis ingestion, led to a review of the literature on this subject. While some clinicians of wide experience appear to have encountered an occasional case, only two published authentic descriptions of this association could be discovered. The earliest such report that came to our notice was that of Recht[1] who observed in two patients that an eosinophilia of from 12 to 18 per cent could repeatedly be induced by the administration of digitalis leaf. More recently Smith and Benner[2] reported in detail a patient in whom recurrences of eosinophilia reaching 30 per cent coincided with successive periods of digitalization.

We believe the following case is an instance of eosinophilia due to digitalis:

CASE REPORT

W. E. M., a white, retired clergyman, aged seventy years, was admitted to the Psychiatric Clinic of the New Haven Hospital on Sept. 12, 1934, because of organic confusion and disorientation.

The family history, as well as the patient's past history, was negative for parasitic infestation, skin diseases, allergic manifestations, migraine, and the convulsive state. Repeated blood examinations of the patient's two children, in consideration of a possible familial eosinophilia, disclosed normal eosinophile counts.

At the age of twenty-eight years the patient developed an acute articular rheumatism which incapacitated him for six months. When he was fifty-five years old, during a short hospital admission for dental surgery, a late systolic murmur was heard at the cardiac apex and was believed to indicate disease of the mitral valve. One year later he returned with cardiorespiratory symptoms, and at this time he presented frank signs of mitral stenosis and insufficiency, with paroxysmal tachycardia, right hydrothorax, and either pneumonia or infarction in the right lung. Under a regime of rest and digitalis therapy good cardiac compensation was regained, and the patient was discharged. A single blood count, which had been done on admission, revealed 2 per cent of eosinophiles.

During the next ten years, from 1920 to 1930, fair cardiac compensation was maintained on 1 gm. of digitalis leaf per week. He was seen twice at intervals of five years because of exacerbations of cardiac symptoms, and on each of these occasions auricular fibrillation was noted clinically and confirmed by the electrocardiogram. Five years before admission the patient suffered arterial embolism in the right foot, followed by pneumonia and herpes zoster. He was treated at home and recovered uneventfully. Except for occasional brief spells of epigastric distress associated with dyspnea and tachycardia, the cardiac course continued satisfactorily on the usual maintenance doses of digitalis.

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During the last decade the patient was subject to brief syncopal attacks unassociated with convulsions, but occasionally followed by temporary confusion and amnesia. Mentally he evidenced a progressive, irreversible organic mental deterioration characterized by irritability, suspicion, fluctuations of the level of consciousness, and defects of memory for recent events. He was finally admitted to the hospital because of the custodial problem he presented.

Physical Examination.—The patient was a well-developed, senile white male in good nutritive state. He was neither dyspneic nor orthopneic; the neck veins were not engorged; and the lips were of good color. There was no edema of the eyelids. The eyegrounds revealed sclerosis of the vessels commensurate with his age; there were no retinal hemorrhages, scars, or exudate. Moderate cardiac enlargement was apparent from the position of the apex impulse in the fifth left intercostal space at the anterior axillary line. The heart sounds were regular, of good quality, and exhibited the typical auscultatory signs of mitral stenosis and insufficiency. Although the right radial pulse was definitely smaller in volume than the left (? old embolus), the blood pressure in each arm was 160 systolic and 90 diastolic. The chest was normal in conformation and mobility, and it yielded a generally resonant note on percussion. The expiratory murmur was slightly prolonged, and a moderate number of medium and coarse crepitant râles were heard over both lower lobes; no musical râles were audible. The liver edge was barely palpable. There was no edema of the extremities or over the sacrum. The skin was loose and inelastic and free from eruption. No muscle tenderness could be elicited. The temperature, pulse, and respirations were normal.

Laboratory Findings on admission revealed a red cell count of 4,790,000 with 107 per cent hemoglobin (Sahli), and a leucocytosis of 12,950 cells per cubic millimeter, of which 22 per cent were eosinophiles. There was a transient albuminuria. The blood Kahn and Wassermann tests were negative. The sputum revealed no acid-fast bacilli, elastic fibers, or Curschmann's spirals; not more than 2 eosinophiles per field were seen with the high power objective. Repeated stool examinations, by concentration methods, were negative for parasites, ova, and blood. Intracutaneous tests with trichiniasis antigen in dilutions of 1:10,000 and 1:500 were negative. The electrocardiogram on Oct. 1, 1934, when the patient was theoretically overdigitalized, revealed only a sino-auricular tachycardia, with a left axis deviation. Another tracing six weeks later, when the patient had theoretically been adequately redigitalized, showed normal and upright T-waves in all leads, and only a very slight depression of the S-T segment in Lead I; the P-R intervals, which had previously been 0.20 sec. in duration, now measured 0.21 sec.

Course in Hospital.—Three days after admission the patient became febrile, and during the next two weeks he ran the typical course of a mild bronchopneumonia. Thereafter he was ambulatory and was without significant cardiorespiratory symptoms practically throughout his three months of hospitalization. However, he did exhibit a persistent, slight expiratory dyspnea together with an occasional moderate afternoon fever. The pulse level varied between 100 and 120 per minute. Because of the persistence of tachycardia and slight basal pulmonary congestion, the maintenance digitalis dosage was cautiously increased from 10 c.c. of the tincture per week to 21 c.c. per week. Although a total of 48 c.c. of the drug was administered during the following sixteen days, there ensued no clinical improvement, change in the pulse, or digitalis intoxication. An electrocardiogram taken toward the end of this period (October 1) gave no evidence of digitalis effect. Throughout this period, both before and during the administration of the excess digitalis, the white cell count remained elevated at 12,000 to 15,000, and the eosinophiles maintained a level around 20 per cent.

Believing that the usual causes for eosinophilia had been excluded and suspecting that digitalis was an etiological factor, we deliberately withheld the drug for

twenty-two days. During this interval the patient's clinical course continued unchanged, but the decline of the eosinophiles to normal levels, as depicted in Fig. 1, was striking. On the resumption of digitalis medication, a new supply of fresh tincture was used, and the eosinophiles again rose rapidly to their previous high level. Although digitalis was again given in unusually large doses (16 c.c. in two days, followed by 3 c.c. daily for seven weeks), there were, as before, no frank clinical or electrocardiographic evidences of digitalis effect. (This same digitalis tincture appeared adequately potent when administered in the usual doses to other patients with congestive failure.)

The mental status was one of apprehension, paranoid delusions, and fluctuating disorientation. The patient was often noisy during the night, and an occasional sedative of 0.6 gm. of barbital was administered. On the night of December 11 he was more disturbing than usual, and the barbital sedative was given twice. The following morning he was stuporous; the pupils were dilated; and the superficial abdominal and deep tendon reflexes were sluggish. During the day the pulse and temperature rose, the breathing became stertorous, and signs of bronchopneumonia appeared. He continued in this state until his death four days later.

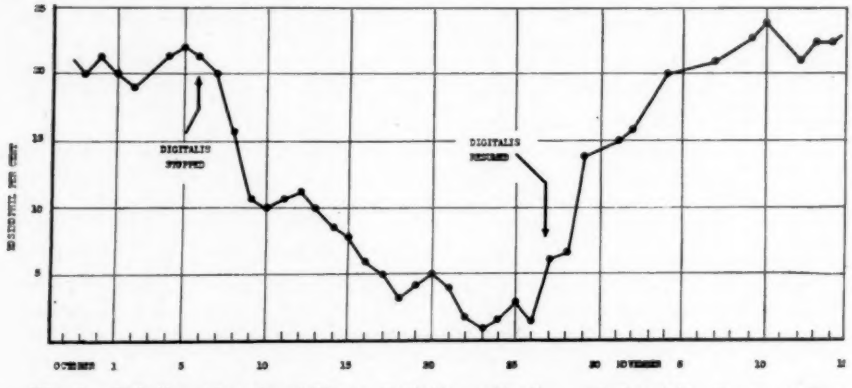

Fig. 1.—Relation of eosinophilia to digitalis medication. Eosinophiles for preceding two weeks averaged 17 per cent and for the succeeding month, 25 per cent.

Necropsy was performed by Dr. Gustave Freeman. The heart with the pericardium weighed 685 gm. and showed moderate hypertrophy of the right auricle and ventricle. An organized mural thrombus occupied the greater part of the left auricle. In addition to stenosis of the mitral valve, there was arteriosclerotic narrowing of the aortic orifice. Microscopically no typical Aschoff bodies were seen. Atheromatous plaques were found in the coronary vessels, and the muscular coats of these vessels here and there harbored groups of small mononuclear cells with bizarre outlines and basophilic cytoplasm.

The lungs felt doughy, the lower lobes were firm, and patches of thickened pleura covered both posterolateral surfaces. The bronchi contained a yellow, purulent material which covered the dark, velvety mucosal lining. Microscopically one could see in the thickened pleura an exudative process with plasma cells and an occasional binucleated giant cell. The pulmonary parenchyma was involved in a fibrosis which was pronounced in several areas; in these regions the enclosed, separated alveoli were lined with cuboidal or columnar epithelial cells. These lesions, which simulated a bronchiolar fibro-adenoma, usually occurred in the vicinity of dilated bronchioles containing purulent exudate and occasionally desquamated epithelial linings. Throughout, one saw focal areas of necrosis with polymorphonuclear exudate. The material which filled the bronchi was peculiar in that the cellu-

lar débris was often arranged in layers of columns which conformed to the longitudinal direction of the tube. A moderate amount of peribronchial muscular hypertrophy was evident. Besides the acute inflammatory process, large numbers of "heart failure cells" abounded. Many of the groups of phagocytes contained large fat vacuoles. The vascular walls were thick and the lumina often diminished.

Both renal surfaces were finely granular, and the capsules were adherent. Hyalinized glomeruli were found in areas of interstitial fibrosis. The liver showed the changes of chronic passive congestion around the central veins. In the brain there was a slight degree of cortical atrophy which was most evident in the frontal lobes. Microscopically, senile plaques and advanced atheromatous changes in the vessels were the only noteworthy changes.

Sections of the deltoid and gastrocnemius muscles gave no evidence of parasites, fibrosis, or inflammation. The other viscera were not remarkable.

DISCUSSION

We believe that the usual causes of eosinophilia have been excluded as factors in the case here presented and that digitalis played an important etiological rôle in the blood dyscrasia. While an eosinophilia associated with, and apparently influenced by, digitalis is in itself a noteworthy phenomenon, even more interesting is the speculation that is aroused as to the nature and mechanism of this response.

Vagotonia appears to be a popular current theory in explanation of some forms of eosinophilia (Schilling[3]). Bertelli, Falta, and Schweeger,[4] first observed that a moderate eosinophilia often followed the injection of pilocarpine, while a diminution in the number of these cells occurred after atropine. Eppinger and Hess,[5] in their monograph on vagotonia, repeatedly mention eosinophilia as a manifestation of this syndrome. More recently Hajós and his collaborators[7] have reported a moderate rise in eosinophilic cells in eight out of ten rabbits during prolonged faradic stimulation of the cut vagi; the responses were small, however, and the observations were not reported in sufficient detail to carry complete conviction. Chillingworth and his collaborators[6] noted a definite eosinophilic cell increase lasting several days in dogs in which partial obstruction to expiration was produced by an intratracheal ball-valve mechanism. They also studied fifteen normal human beings and detected an immediate, slight but definite rise in eosinophiles apparently produced by the resistance to expiration offered by a partially blocked flutter valve through which the subjects breathed for only a few minutes. These observations were regarded as evidence of a vagotonic basis for eosinophilia, and the mechanism was explained with the theory that the initiating factor was an overdistention of the alveoli which, through vagus stimulation, ultimately brought about a release of eosinophiles from blood-forming organs or blood reservoirs. Furthermore, the authors offered in their experiments an explanation to replace the older "blood acidity" theory of eosinophilia. Pescatori[7] was the first to state the belief that the increased carbon dioxide content of the blood in the "partial asphyxia" of asthma and emphysema constituted

a specific stimulus for eosinophile production. Banerji's experiments[8] are sometimes cited in substantiation of this theory, but the very slight eosinophilic cell increases he observed in a few rabbits which were subjected to asphyxia were not at all convincing. Chillingworth and his associates argue that it was not the increased blood carbon dioxide resulting from respiratory obstruction, but rather the associated alveolar distention which constituted the important eosinophile-stimulating fac-

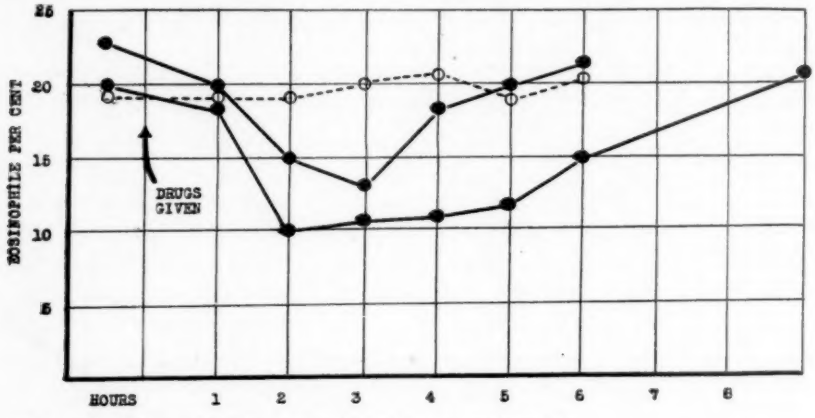

Fig. 2.—Effect of atropine and pilocarpine on eosinophilia.
●——● Atropine sulphate (0.9 mg.) injected on two occasions.
o_____o Pilocarpine hydrochloride (0.5 mg.).

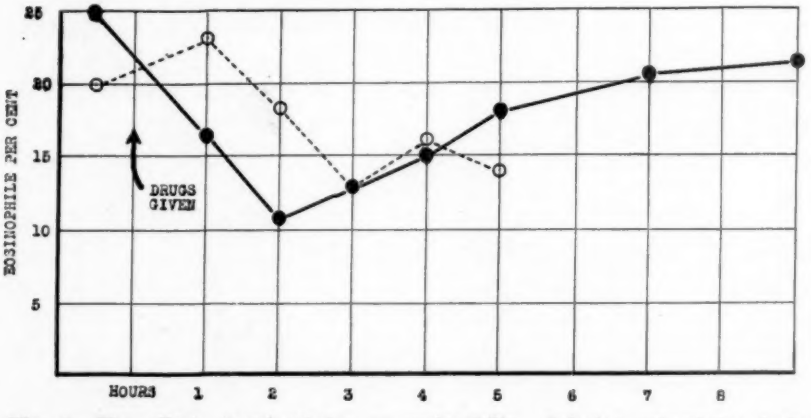

Fig. 3.—The effect of epinephrine on eosinophilia. Injected epinephrine hydrochloride (1:1000 dilution):
o_____o Effect of 0.5 c.c.
●——● Effect of 0.75 c.c.

tor. In corroboration they state their observation that in uncomplicated emphysema no eosinophilia is observed in spite of the elevated carbon dioxide tension which prevails in this condition.

Consistent with the vagotonic theory of eosinophilia would be the diminution in number of these cells caused by either adrenalin or atropine, and their increase by pilocarpine or choline esters. Such

effects with pilocarpine and adrenalin were observed by Wieck[9] in a patient with vagotonic manifestations who exhibited a persistent but obscure eosinophilia. Our patient was injected on different days with 0.5 mg. pilocarpine hydrochloride, twice with 0.9 mg. atropine sulphate, and on two occasions with adrenalin hydrochloride solution. Although no unusual reactions occurred with any of these drugs, the depression of the eosinophile level by both adrenalin and atropine seemed definite, while with pilocarpine there was no apparent effect (Figs. 2, 3). Unfortunately, a choline preparation was not available in time for trial. Smith and Benner[2] likewise noted a fall in eosinophile percentage after therapeutic doses of adrenalin and atropine, but no change following pilocarpine.

Although it is inviting to invoke the vagal effects of digitalis in explanation of the eosinophilia in our case, it is noteworthy that the patient appeared actually refractory to the drug. The rate and character of the pulse were not influenced by excessive doses of the drug; the electrocardiographic films indicated no digitalis effect even after presumably toxic doses had been given; and there was no decline in the patient's clinical state during the three-week period when digitalis was entirely withheld. That digitalis, rather than pulmonary pathology, was the principal etiological factor in the eosinophilia would seem probable in view of the striking alterations in the level of these cells coincidental with digitalis administration and withdrawal.

SUMMARY

A case of eosinophilia presumably due to digitalis is described, and the alleged vagotonic mechanism of the blood response is discussed.

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FUNCTIONAL CAPACITY OF THE NORMAL PERICARDIUM

An Experimental Study*

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IN THE normal animal the limits to which the heart can rapidly dilate are fixed by the capacity of the pericardial sac; since Barnard[1] in 1897 showed experimentally that the pericardium is a practically inelastic structure and its capacity is therefore relatively fixed as far as acute distention is concerned. Accordingly, the question arises as to what extent the pericardium normally restricts the ability of the heart to dilate and, from the clinical standpoint, whether it is worth tapping relatively small pericardial effusions when they occur within a short space of time, e.g., as a result of trauma. In this connection it must be emphasized that this study concerns itself only with rapidly accumulating effusions as best exemplified by trauma and not those occurring more slowly as the result of inflammatory process where large effusions can occur (e.g., 1,500 to 2,000 c.c. or more). This entire subject has been studied from a number of angles, but the conclusions have not been entirely concordant (see review by Wiggers[17] in 1929).

Barnard[1] in 1897 showed that at constant high venous pressures removal of the pericardium increased the filling of the ventricles to a marked extent, and similar observations were made by L. Hill[7] and by Evans and Matsuoka.[4] Kuno[9] in 1917 using heart-lung preparations found that even from 3 to 5 c.c. of fluid introduced into the pericardial sac of the dog caused an increase in the venous pressure and a decrease in the output of the left ventricle, and he concluded that the pericardium exercises, under every condition of venous inflow, a certain amount of resistance to diastolic expansion of the heart.

Van Liere and Allen[15] in 1927 and Van Liere and Crisler[16] in 1930 concluded from their experiments on acute cardiac dilatation in dogs that the pericardium might have a protective action in conditions of extreme stress on the heart. Rossler and Unna[13] in 1935 claimed that the pericardium in acutely damaged hearts prevents overdistention of the right heart.

The mechanism of any restraining action which the pericardium might have was studied by Wilson and Meek[18] in 1927. They found that the restraining influence of the pericardium was abolished when the pericardio-diaphragmatic attachments were cut and hence attributed any interference which the pericardium might exert on cardiac filling, not

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to a lack of space but to diaphragmatic pull drawing the upper lateral walls over the auricles and thereby reducing their filling. From their observations it seemed that the limits of pericardial capacity were reached in normal dogs when the effective venous pressure was increased to three times its normal value.

On the other side of this question, observations have been advanced to show that there is ample room for diastolic distention within the pericardium. Thus Henderson and Prince[6] found by autopsy measurements in human beings that the average capacity of the pericardial sac (including the capacity of the heart itself) was from 3.5 to 5 c.c. per kilogram of body weight, and since the maximum stroke volume never exceeds 2 c.c. per kilogram, they concluded that a considerable margin was left for further dilatation.

Also it has been shown that removal of the pericardium produces no demonstrable effects. Mazzone[10] in 1912 and Rehn[12] in 1913 studied dogs in which the pericardium had been removed and found no ill effects on the health of the animals. Beck and Moore[2] in 1925 removed the pericardium in five dogs and subjected them to severe exercise. They found that these animals responded very well to exercise. Furthermore, a number of clinical cases of partial or total congenital absence of the pericardium without producing any clinical symptoms have been reported.[11, 5]

In order to determine the capacity of the pericardium, experimental injection of the normal human pericardial sac after death has been carried out. These experiments showed that from 150 to 200 c.c. of liquid completely filled the complementary spaces of the pericardium and distended the sac.[3] However, this does not necessarily correspond to conditions in the living.

As far as actual measurement of the capacity of the pericardium of living animals is concerned, the reported observations are not very numerous. Starling[14] in 1897 reported observations on one living dog in which he found that injection of 40 c.c. of oil into the pericardial sac caused a slight rise in venous pressure and that injection of 70 c.c. of oil caused in addition to a marked rise in venous pressure, a fall in arterial pressure. Katz and Gauchat[8] in 1924 injected oil and also saline into the pericardial sacs of dogs in amounts up to 120 c.c., obtaining a rise in venous pressure, a fall in blood pressure, and a pulsus paradoxus; but they did not note the point at which the venous pressure first began to rise.

It was our purpose to carry these observations further by determining the amount of fluid that could be introduced into the pericardium of living dogs without interfering with the function of the heart in any way.

METHOD

The effective capacity of the pericardium was measured directly in twenty living dogs. This was done by allowing warm saline solution to run from a buret through a special cannula into the pericardial sac. The height of the venous pressure was meanwhile measured by means of a water manometer connected with a cannula inserted through the external jugular vein into the superior vena cava.

It has been demonstrated experimentally that a rise in venous pressure is the first effect produced by increasing the pressure in the pericardial sac. This is followed by diminished ventricular filling and a fall in blood pressure. By the method outlined above, we were able, therefore, to determine the maximum volume of warm saline that could be introduced into the closed pericardial sac without producing an impairment of cardiac filling.

Measurements were made on twenty dogs with normal venous pressures, shortly after complete barbital anesthesia and opening of the chest. The pericardio-diaphragmatic attachments were left intact. During the tests artificial respiration was so regulated that the dogs just failed to breathe naturally.

RESULTS

The results obtained are shown in Table I. The dogs' weights varied between 7.5 and 17.0 kg., the heart weights between 64 and 167.5 gm. and the amounts of warm saline that could be introduced without any interference to ventricular filling varied between 21 and 79 c.c. A study of these results shows at a glance that a general relationship exists be-

TABLE I

EXPER. NO.	WT. OF DOG IN KG.	WT. OF HEART IN GM.	CAPACITY OF PERICARDIUM IN C.C.	RATIO— HEART WT.: PERICARD. CAP.
1	10.2	89	30	3:1
2	11.75	120	33	3.6:1
3	7.5	67	21	3.2:1
4	15.75	145	56	2.6:1
5	12.5	70	30	2.3:1
6	--	90	29	3.1:1
7	14.0	105.5	75	1.4:1
8	16.5	162	79	2.1:1
9	13.5	115	40	2.9:1
10	8.5	64	42	1.5:1
11	9.5	93	44	2.1:1
12	14.5	177	45	3.9:1
13	15.0	108	27	4:1
14	17.0	152	44	3.5:1
15	12.25	140	48	2.9:1
16	12.0	108.5	39	2.8:1
17	13.5	117	48	2.4:1
18	10.5	115	32.5	3.6:1
19	15.5	167.5	44	3.8:1
20	11.5	77	34	2.3:1
Average—Heart Weight: Pericardial Capacity = 2.9:1				

tween heart weight and body weight on one hand and pericardial capacity on the other. Considerable variation in this ratio occurred, however, in different animals. This was to be expected in view of the different types of dogs used and their different antecedent histories (some of them probably had led very inactive lives while others might even have been used on the race track). The ratio of heart weight to pericardial capacity varied between 1.4:1 and 3.9:1, but the majority ranged around a 3:1 ratio. If these ratios are applicable to normal human hearts weighing 250 to 300 gm., then a pericardial capacity in human beings of about 80 to 100 c.c. can be inferred. This may be an indication of the size of rapidly accumulating effusions which might embarrass the heart.

Since the values obtained experimentally in dogs and those inferred for man are greater than the systolic discharge of the heart (which in man according to Grollman averages about 62 c.c.), the conclusion is justified that the pericardial sac offers an ample margin by which the normal heart may dilate.

SUMMARY

1. Measurements were made of the amount of saline which could be introduced into the pericardium of each of twenty living dogs before a rise in venous pressure occurred.

2. The amounts which could be introduced varied between 21 and 79 c.c.

3. The ratio of the heart weight to pericardial capacity varied between 1.4:1 and 3.9:1, but in the majority of instances was about 3:1.

4. Applying this ratio to normal human hearts a human pericardial capacity of about 80 to 100 c.c. can be inferred.

5. The pericardial sac offers an ample margin by which the normal heart may dilate.

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Department of Clinical Reports

ANOMALY OF THE RIGHT CORONARY ARTERY IN A YOUNG PATIENT WITH AORTIC VALVULAR DISEASE, CARDIAC ENLARGEMENT, AND ANGINA PECTORIS*

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ANOMALIES of the coronary arteries are sufficiently unusual to justify placing on record this case of duplication and stenosis of the right coronary artery with abnormal distribution of the vessels.

CASE REPORT

C. H., male, aged sixteen years, was admitted to the charity service of Baptist Memorial Hospital (28,896) Nov. 13, 1930, on the service of Dr. John Maury, Jr. He gave the history of an attack of rheumatic fever with heart involvement in 1924. About two and a half years before admission, while in bed with pleurisy, he had some palpitation. After six weeks in bed, he returned to school, but this effort caused palpitation and some dyspnea and precordial pain which gradually grew worse. He was examined and sent to a hospital in Kansas City.

In 1929 he began to have severe pain about his heart, that radiated down his arms. At the beginning these pains occurred weeks apart, but gradually they appeared more frequently, until on admission he was having from 3 to 5 attacks in twenty-four hours. The pain was very severe, lasting on the average about an hour, but in one instance lasting four hours. Morphine seemed to relieve the pain, and he had taken as much as 1 grain at a time to obtain comfort.

He also complained of rapid heart action, the shock of the heartbeat against the chest wall, and of swelling of the feet.

Physical examination revealed an anemic and undernourished boy, with a marked precordial bulge, pulsation, and shock. Visible pulsations were noted in the neck and abdomen. The heart was greatly enlarged, the apex beat being in the midaxilla, seventh interspace. Systolic and diastolic murmurs were heard over the heart, especially at the aortic area, and were transmitted to the neck. The rate was 100-120, rhythm regular. He had a water-hammer pulse. The blood pressure was 140/20 in the right arm, 80/10 in the left.

Laboratory tests at this time showed: red cell count, 3,960,000; hemoglobin (Sahli) 65 per cent; white cell count and differential count were normal. Urinalysis was negative; blood Wassermann, negative; and blood culture, negative (six days).

The electrocardiogram showed a heart rate of 100, with a normal rhythm. P_2 was notched; the QRS complex was widened (0.1-0.12 sec.), was upright, was slurred and notched in Lead I, upright and slurred in Lead II, and diphasic in Lead III. T_1 was inverted; T_2, diphasic; T_3, upright. My impression was that there was left ventricular preponderance with probable coronary obstruction.

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The teleroentgenogram gave these measurements: RM, 7 cm.; LM, 8.8 cm.; transverse, 15.8 cm.; length 18.5 cm.; transverse aorta, 8 cm.; internal thoracic diameter, 22.7 cm.

On December 13, Dr. R. Eustace Semmes attempted alcoholic injections of the paravertebral nerve areas, but because of a moderate scoliosis of the cervical spine, this was not successful. There were no areas of anesthesia present the next day, and no apparent relief of symptoms.

On December 15 the following was reported: "X-ray films of the cervical and dorsal spine showed some arthritic changes in the dorsal portion, not extensive, considerable curvature of the spine, with lordosis in the cervical area."

In January he suffered from a feverish "cold," during which the heart pain disappeared.

On January 26, 1931, Dr. Semmes operated on him and cut the sensory nerve roots under novocaine anesthesia. Laminectomy of last cervical and first two dorsal vertebrae was performed. The dura was opened, exposing the cord. When the nerve roots were stimulated, the patient identified the sensory roots of the last cervical and first three dorsal segments (and only these) as those conducting the pain. These roots were severed.

The operation was followed by extreme pain in the chest, probably due to a pericarditis, as evidenced by a friction rub.

For a week after the operation there was no angina. Four or five times a day, however, he suffered from a "heavy, smothering feeling" in the left chest. This was considered to be an anginal equivalent. There remained some sensation to touch and pressure over the left side of the chest, but less than on the right.

In early February he had mild bronchopneumonia.

About February 21 for a few nights he had anginal attacks over the heart and down the left arm. He thought there was some vague, inexplainable difference between these and the previous spells. There was not much numbness or alteration in sensation over the chest. At the sixth rib and below on the left there was distinct hyperesthesia. It was surprising there was not more sensory loss, but because of his severe illness and the frequent use of drugs, it was not certain that his full cooperation was obtained.

He was discharged to his home but reentered the hospital March 28 on the service of Dr. William C. Colbert. His condition got worse at home, and he had two or more severe anginal spells a day.

On April 6 he went into a coma and died.

Clinical Diagnosis.—Rheumatic heart disease, cardiac enlargement, aortic and mitral valvular disease, coronary sclerosis, angina pectoris, dilatation of aorta (ascending).

Autopsy was performed on April 6, 1931, by Dr. N. E. Leake and the author. The body was that of a white male, presenting evidence of emaciation and marked anemia. There was no edema. There was bulging of the precordium with a marked deformity of the chest framework. A linear scar over vertebral column extended from the lower cervical region downward about 4 inches.

Chest.—The bulging precordial area was due to an enormous heart, which weighed 740 gm. The relationship of this organ to the chest cavity was normal except for its size. The base of the heart extended well up into the upper portion of the right chest while the apex reached in the left lower chest to a level of the seventh rib in the anterior axillary line. No pericardial adhesions were present, but there was 160 c.c. of yellowish, amber, turbid fluid in the pericardial sac. The ascending portion of the aortic arch was somewhat dilated. The heart was removed and examined; the following findings resulted: The wall of the right ventricle was poorly developed and very thin, 5 mm. at the thickest part, 1.5 to 2

mm. at the thinnest. The tricuspid valve was normal. Right auricle was normal except for thin wall, and slight dilatation. The left ventricle showed marked hypertrophy and dilatation, the ventricular wall being 19 mm. thick. The aortic valve leaflets were thick but not adherent, but the thickness and stiffness caused some degree of aortic stenosis, and their retraction permitted considerable regurgitation. The mitral valve was slightly thickened in some portions and moderately so in others, and it was also retracted. There were no fresh vegetations on either valve. On the wall of the aorta, which was otherwise smooth and glistening, there were two slightly elevated, soft pinkish gray areas, translucent, about 1 cm. in diameter, suggestive of sessile vegetations. These did not involve the mouths of the coronary arteries.

The left coronary orifice measured 5 mm. in diameter. The coronary artery itself when opened measured 14 mm. in circumference. The wall was smooth, and there were no abnormalities as far as the vessels could be traced.

Fig. 1.—Drawing illustrating the anomalous openings of the right coronary artery (*A*), and the short vessel coming from the smaller opening (*B*). The thickening and retraction of the aortic cusps is also shown. The drawing was made from the fixed specimen by J. L. Scianni, M.D., of the Art Department, Division of Pathology, College of Medicine, University of Tennessee.

The orifice of the right coronary artery was double, the larger aperture measuring 2 mm. in diameter, the smaller about 0.75 mm. in diameter. (Fig. 1.) These apertures led into separate vessels that had no connection. The circumference of the larger of the two was 9.5 mm. The vessel was otherwise normal except for its distribution. The smaller aperture led into a fair sized vessel (record of measure lost) which after a course of an inch and a half plunged boldly into the musculature.

The lungs presented evidence of moderate chronic passive congestion at the inferior pole of the right lower lobe.

All abdominal viscera presented chronic passive congestion. No increase in intraperitoneal fluid was noted. The liver was greatly enlarged and unusually dark reddish blue in color. The spleen was enlarged, similar to the liver in color. No abdominal viscera were disturbed.

Anatomical Diagnosis.—Congenital malformation (duplication and stenosis of the right coronary orifice). Abnormal distribution of the right coronary vessels. Stenosis and regurgitation of the aortic valve, probably rheumatic in origin. Slight thickening of mitral valve (with insufficiency). Dilatation and hypertrophy of the left ventricle. Fresh vegetations on aortic wall. Chronic passive congestion of lungs and all abdominal viscera.

COMMENT

Bland, White, and Garland[1] have recently reviewed the cases of congenital anomalies of the coronary arteries. They grouped them into two main headings, (a) abnormalities of origin and (b) variations in number, size, and distribution. The latter group, to which the present case belongs, is of less importance clinically, since certain types are not incompatible with long life. It is quite possible that this patient would have survived for many years had he not had the additional disabling factor of acquired rheumatic valvular disease.

The first representations of the coronary arteries in the embryo are endothelial cushions, which become columns and grow out into the superficial portion of the myocardium. These columns then become hollow. It takes but little imagination to conceive of a part of a primary cushion becoming separated from the main portion and developing into an independent artery alongside of the parent. Whatever factors cause this separation may be effective also in guiding the growing artery into abnormal pathways, so that the distribution is unusual as well as manner of origin. In this case, the vessels apparently were of sufficient size to convey enough blood to the right ventricle, but the orifices were small, together being distinctly less than the normal. This functional stenosis leading to inadequate blood supply to the right ventricle was no doubt the cause of its thin wall.

SUMMARY

A case is reported of a congenital doubling of the right coronary artery, with stenosis of the orifices, associated with rheumatic aortic valvular disease, angina pectoris, and enlargement.

Thanks are due to Dr. R. E. Semmes, who performed the alcohol injections and the nerve root sections; Dr. N. E. Leake, who performed the autopsy with me; Dr. John Maury, Jr., and Dr. William C. Colbert, who permitted me to study this patient while on their services.

REFERENCE

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Department of Reviews and Abstracts

Selected Abstracts

Code, Charles F., Dingle, W. T., and Moorehouse, V. H. K.: The Cardiovascular Carotid Sinus Reflex. Am. J. Physiol. **115**: 249, 1936.

A study has been made of the anatomy of the carotid sinus region of the dog in order to determine the nerves ending in the carotid sinus. The physiological function of the nerves supplying the sinus has been investigated and the following results obtained.

Anatomically, it has been found that the carotid sinus possesses three sources of nerve supply: a branch from the posterior division of the glossopharyngeal nerve, a branch from the superior cervical ganglion, and a small nerve which accompanies the internal carotid artery.

Electric stimulation indicates that the nerve accompanying the internal carotid artery is not concerned in the carotid sinus reflex.

A study of the comparative responses of the sympathetic nerve and the sinus nerve to electric stimulation clearly indicates the greater importance of the sinus nerve.

On the basis of acute and survival denervation experiments it is concluded that the cardiovascular components of the sinus reflex are conducted solely through the sinus nerve.

Evulsion of the sinus nerve is submitted as a method of carotid sinus denervation, and the surgical approach to the sinus nerve is described.

These experiments lend support to the view that the carotid sinus operates entirely through a depressor mechanism.

AUTHOR.

Krass, Ernst: The Effect of Electric Current on Intravascular Clots in Animal Experiments. Arch. f. klin. Chir. **184**: 383, 1936.

The effect of passing an electric current through experimentally produced intravascular clots was studied to determine whether fixation of the clot to the vessel wall could be attained as a step toward the prevention of embolism. The clots were produced by injecting sodium morrhuate solution into the jugular veins of dogs. Direct current of varying intensity and for different periods was passed through the occluded segment of the vessel. In that portion of the vein which was directly in contact with the cathode, the clot became retracted, softened, and firmly attached to the intima. No such changes occurred at the anode. Similar results were obtained if the cathode was placed on the skin overlying the occluded vein. Rapid organization of the clots followed with restoration of the vascular lumen.

L. M. Z.

Doering, B.: Experimental Production of Hypertrophy of the Left Heart in Rabbits by Ephedrine and Ephetonin. Beitr. z. path. Anat. u. z. allg. Path. **96**: 309, 1936.

Fourteen rabbits were injected subcutaneously with ephedrine or ephetonin daily for 44 to 154 days except for irregularly interposed rest periods of a day to avoid

immunization. The dose was 0.05 gr. per day. As a result, the blood pressure increased markedly in the first period of the experiment, but decreased slowly after about 100 days to the normal and could not be raised again with repeated injections. Rabbits killed during the high pressure period generally showed a distinct hypertrophy of the left and a slight hypertrophy of the right ventricle. Four animals were killed a long time after the high pressure period was over. No hypertrophy of the ventricles was found in these rabbits.

The author believes he has proved the possibility of the return of the hypertrophic heart to a normal size after eliminating the cause for the hypertrophy.

A. V.

Plá, Juan Carlos and Fabregat, Agosto: Syndrome Characterized by Simultaneous Crisis of Tetany and Paroxysmal Tachycardia. Rev. argent. de cardiol. **2**: 265, 1935.

A case is reported of a woman affected by parathyroid insufficiency who showed simultaneous attacks of tetany and paroxysmal tachycardia. The progress of the patient and the success obtained with an adequate treatment warrant the following statements:

a. Paroxysmal tachycardia may be a clinical manifestation of parathyroid insufficiency.

b. There can be a coexistence of paroxysmal tachycardia and tetany.

c. Parathormone may in these cases (as in this one) cure the paroxysmal tachycardia.

H. McC.

Finkelstein, Leonard E.: Cardiomegalia Glycogenica Circumscripta. Am. J. Med. Sc. **191**: 415, 1936.

A case of idiopathic hypertrophy of the heart, reported in 1924 by Carrington and Krumbhaar, is reviewed. Histologically the myocardium showed many areas of apparent vacuolization similar to those found in the cardiac type of von Gierke's disease. Moreover, the presence of glycogen can be demonstrated in this specimen.

Such localized deposits of glycogen in an otherwise unexplained hypertrophy of the heart may represent a localized form of von Gierke's glycogen storage disease, or a healing stage of that disease, or merely a cause of idiopathic hypertrophy.

The descriptive term "cardiomegalia glycogenica circumscripta" is suggested for this condition.

AUTHOR.

Coronini, C., Popper, H., Neugebauer, R., and Piringer, W.: Postmortem Blood and Organ Cultures of Acid-Alcohol Fast Bacilli in "Rheumatic" Heart Disease. Virchows Arch. f. path. Anat. **296**: 422, 1936.

Cultures of the blood and organs were made of 161 persons who died of rheumatic heart disease. A total of 588 organ cultures and 166 blood cultures were made.

It was found that the more acute the rheumatic heart disease was, the higher was the percentage of tubercle bacilli found in cultures: in 18 cases of acute and subacute rheumatic endocarditis, 10 were positive; in 15 cases of chronic recurrent endocarditis, 7 were positive; in 45 cases of valvular insufficiency with superimposed acute verrucous endocarditis, 15 were positive; in 57 cases of old endocarditis without recent changes, only 7 were positive. Even cases of subacute ulcerative endocarditis showed positive cultures.

In most cases the bacilli so obtained caused typical tuberculosis when injected into guinea pigs.

The highest percentage of positive cultures was obtained from the tonsils and the myocardium. Less often positive cultures were obtained from the spleen and the blood, and in two cases positive cultures were obtained from the endocardium.

The authors conclude that the tubercle bacillemia found in these cases is a secondary invasion of the bacilli into the blood which in hyperallergic subjects manifests itself as rheumatic disease. Cocci, which also were frequently found in the cultures, are regarded by the authors as of secondary importance.

A. V.

Von Rutich, E.: The Duplicated Sound in the Auscultatory Method of the Blood Pressure Determination. Klin. Wchnschr. **15**: 54, 1936.

In the auscultatory method of blood pressure determination, a duplication of arterial sounds is frequently heard for some time between systolic and diastolic pressures. This duplicated sound can be detected over the cubital or popliteal arteries of both normal and sick subjects. It is inconstant and bears no relationship to any specific pathological process. The author suggests that this phenomenon is produced by the contour of the pulse wave. The two phases of the arterial wave stretch the arterial wall at the lower edge of the cuff twice in quick succession and set up the vibrations.

R. K.

Arnott, W. M., and Kellar, R. J.: The Effect of Renal Denervation on the Blood Pressure in Experimental Renal Hypertension. J. Path. & Bact. **42**: 141, 1936.

Bilateral nephrectomy did not lead to hypertension in the rabbits which survived the operation; on the contrary, a progressive fall was observed. Sodium oxalate nephritis had been found previously to cause hypertension in animals; it failed to alter the blood pressure curves in bilaterally nephrectomized animals, causing the authors to conclude that its effect is due to renal damage.

Denervation of the kidney abolishes the hypertension of oxalate nephritis in animals in which one kidney remains intact.

L. H. H.

Sansum, W. D.: The Favorable Influence of Adequate (Higher) Carbohydrate Diets on the Blood Pressure of Diabetic Patients. South. Med. J. **29**: 414, 1936.

In addition to the beneficial effect of the high carbohydrate diet on the incidence of ketosis, and on the state of nutrition with minimal insulin dosage, Sansum here states that "the incidence of premature arteriosclerosis is being prevented in children." The factor implicated in the older diabetic diets seems not to be the acid-base balance, but the high cholesterol content. The author writes of the effects on arteriosclerosis; the reader must presume that hypertension, indicated in the title, always accompanies the arteriosclerosis.

L. H. H.

Hines, E. A., Jr., and Brown, George E.: Arteriolar Hypertonus Without High Blood Pressure (Latent Hypertension). Proc. Staff Meet., Mayo Clin. **11**: 21, 1932.

The authors have observed middle-aged and elderly patients who had a hypertension type of sclerosis affecting the arterioles but who did not have hypertension. Fifty such patients were subjected to a special study of their blood pressure reactions. Each patient was subjected to a cold pressor test, and on ten patients hourly readings of blood pressure were carried out. All of the subjects gave a

definite hypertensive type of reaction to the cold pressor test. The mean reaction in blood pressure for the group was 38.4 mm. of mercury, systolic, and 26.4 mm., diastolic. In 70 per cent of the cases the return to the previous basal level was prolonged abnormally. The hourly reading of blood pressure revealed marked lability in each of the ten cases studied in this manner. The lability was in the lower ranges as compared to the lability in the higher ranges of subjects with essential hypertension. There was a family history of hypertensive cardiovascular disease in 82 per cent of the cases.

These studies suggest that such patients have a latent or subclinical form of hypertension. They display an abnormality of the blood pressure, manifested by momentary hypertension and excessive responses to stimulation. This hyperreaction of the blood pressure is indicative of an arteriolar hyperactivity. The authors believe that the arteriolar hyperactivity is the mechanical factor producing the changes in the arterioles. The appearance of these manifestations may precede the clinical stages of essential hypertension.

AUTHOR.

Allen, Edgar V.: How Arteries Compensate for Occlusion: An Arteriographic Study of Collateral Circulation. Arch. Int. Med. 57: 601, 1936.

The arteriograms show evidence of profuse collateral circulation in cases of occlusive arterial disease. Logical and purposeful design in the development of collateral circulation is apparent. By methods which have been designated as anastomosis, lateral projection, prolongation, terminal branching, and network formation, a collateral circulation develops which can compensate for extensive occlusion of the chief arteries of an extremity. There is indirect but entirely logical and convincing evidence that collateral arteries are chiefly arteries which are present normally but which have increased in size as a response to a demand for increased function which arises as a result of occlusion of the main arteries.

AUTHOR.

Wilson, Harwell, Roome, Norman W., and Grimson, Keith: Complete Sympathectomy: Observations of Certain Vascular Reactions During and After Complete Exclusion of the Sympathetic Nervous System in Dogs: an Experimental Study. Ann. Surg. 103: 498, 1936.

Observations upon the blood pressure of normal dogs during the three stages of complete sympathetic exclusion showed that the blood pressures tend to recover after each stage of sympathectomy; however, there was no evidence of marked overcompensation; that is, there was no significant rise of blood pressure above the normal. After the right thoracic chain was removed, half the animals maintained a blood pressure very slightly above normal, and one-half fell below, but all were within the normal range. Following removal of the left thoracic chain with section of the greater splanchnic nerve, the greatest and most continued depression occurred. Abdominal sympathectomy usually produced no significant change in the blood pressure. Six of the animals upon which complete sympathetic exclusion had been performed were kept for periods of many months, and all have shown blood pressure recovery that casts doubt on the idea of maintained hypotension following any type of sympathetic surgery. The animals studied, however, were normal, while surgical procedures which have been described by various authors are directed toward lowering an abnormally high arterial tension. The depression of the blood pressure which follows section of the cervical spinal cord, and high spinal anesthesia in normal dogs, was absent in recently completely sympathectomized animals. This finding agrees with the commonly accepted idea that the depressor effect of these two procedures is due to the removal of tonic vasoconstrictor impulses passing

down the cord from the vasomotor center and leaving it by the thoracolumbar outflow. The transient rise of the blood pressure which may occur at the moment of section of the spinal cord of normal dogs was also absent in the sympathectomized animals. Both these observations suggest that in recently sympathectomized animals there is no important vasoconstrictor outflow from the spinal cord below the first dorsal segment and that in the intact animal all such outflow is carried through the sympathetic chains.

Comparison of the blood pressure maintained shortly after sympathectomy with the blood pressures resulting immediately from high spinal anesthesia and cervical cord section in normal dogs indicates the presence in the former condition of some factor maintaining the blood pressure at a higher level than in the latter conditions, although in all there is presumably nearly complete loss of vasomotor tone. Sympathectomized animals with lowered blood pressures had bleeding volumes which were approximately normal, which suggests that such animals should withstand hemorrhage, trauma, or an operation approximately as well as normal dogs.

The blood pressure after complete sympathectomy remains at a higher level than would be expected after withdrawal of all vasoconstrictor tone. The possibility of a peripheral vasoconstrictor mechanism is suggested.

E. A.

Nagy, Michael: Operatively Healed Case of a Symptomatic Raynaud's Disease Caused by a Cervical Rib. Monatschr. f. Psychiat. u. Neurol. **91:** 300, 1935.

The right hand of a farmer, fifty-six years old, was cold and painful. The typical spastic attacks were absent. The finger tips were cyanotic. The radial pulse was absent. X-ray examination showed a cervical rib 8 cm. long. After resection of the cervical rib most of the vascular disturbances disappeared. It would seem that in this case they were caused by the pressure of the cervical rib on the brachial nerve plexus.

J. K.

Bierman, W.: The Temperature of the Skin Surface. J. A. M. A. **106:** 1158, 1936.

A detailed report is made of the results of skin temperature readings of all parts of the body under varying conditions of health and disease, both from personal observation and from many sources in the literature.

Aside from the obvious usefulness of such readings in peripheral vascular disease (separating spastic from organic occlusion), their value in other disease conditions, and in estimating the influence of drugs and physical measures, is considered.

L. H. H.

Alcock, P., Berry, J. L., and Daly, De Burgh: The Action of Drugs on the Pulmonary Circulation. Quart. J. Exper. Physiol. **25:** 369, 1935.

Studies were made on the isolated lung preparations of the dog under negative pressure ventilation and perfused with defibrinated blood. Acetylcholine in the smallest effective doses causes a slight fall in pulmonary arterial pressure, and in large doses a rise in pulmonary arterial pressure. The effects are in part, if not solely, independent of bronchomotor mechanisms. The pulmonary arterial pressure rise or fall due to acetylcholine injections occur in nicotinized preparations, are enhanced by eserine and suppressed by atropine. Adrenalin in small doses may have no effect upon the pulmonary arterial pressure and yet cause an increase in venous outflow. A method is described for measuring the blood inflow and outflow from lungs under negative pressure ventilation.

E. A.

Meyer, Fritz: The Causes of Oxygen Deficiency in the Tissues of Patients with Circulatory Diseases. Klin. Wchnschr. 15: 48, 1936.

An insufficient supply of oxygen in the tissues in circulatory diseases may be due to three different causes: (1) an insufficient oxygenation of the arterial blood (detected by blood gas analysis), (2) a sluggish capillary circulation, and (3) a decreased permeability of the wall of the capillaries to oxygen.

The differential diagnosis between the latter two can be made by determinations of the CO_2 and O_2 tensions in the tissue, following a method described previously by the author. When capillary circulation is slowed, the O_2 tension in the tissue is diminished, and the CO_2 tension is increased. The difference between the gas tensions of the tissues and of the capillaries is not changed. A disturbance of the permeability of the capillaries produces a different picture. The O_2 tension in the capillaries remains normal, but decreases in the tissues. The CO_2 tension in the tissue is only slightly increased. The differences in the tensions between the tissues and the capillaries are markedly increased for O_2 and slightly for CO_2. The results are summarized by means of a special nomogram. Only two of the fourteen patients with circulatory diseases had a decreased permeability of the capillaries to oxygen.

R. K.

Gauer, Otto: The Velocity of Pulse Wave in the Aorta and Femoral Artery of Human Beings. Ztschr. f. Kreislaufforsch. 28: 7, 1936.

Measurement of the velocity of pulse wave in the aorta and femoral artery in a healthy person twenty-four years of age was determined with the following results: In the thoracic aorta in a standing or reclining position the rate was 3.8 to 4 meters per second. It increased in the abdominal aorta to 4 to 4.5 meters per second. In the femoral artery, in a standing position, the rate was 12 to 13 meters per second, and in a reclined position 8.5 meters per second. Control examinations on other individuals showed only a slight variation from these findings.

J. K.

Gartner, Wilhelm: The Clinical Picture and Circulatory Disturbances in Paraganglioma of the Adrenals. Ztschr. f. Kreislaufforsch. 28: 82, 1936.

The author assembles and critically analyzes twenty-two cases from the literature. He finds that the tumor is unilateral, usually on the right side, and that it rarely metastasizes. All patients have paroxysmal hypertension with the pressure going up as high as 300 systolic; these attacks, as time goes on, increase in frequency and intensity. There are usually several attacks a day; the patient between attacks appears to be normal. The patients have hemorrhages, especially from the nose or into the retina with consequent visual disturbances. They complain of pain over the entire body, especially in the back over the adrenals. Glycosuria occurs only during an attack. Chronic hypertension may eventually appear, or the pressure between attacks may remain normal. Apoplexy may occur during an attack, manifesting itself by unconsciousness, motor unrest, epileptiform movements, or visual disturbances. Such an event may lead to the mistaken diagnosis of glomerulonephritis. The patient may recover from the apoplectic seizure, but a succeeding one may cause death. In several patients death was preceded by coma. Treatment consists in removing the tumor, and in several instances this procedure was followed by complete cure.

L. N. K.

Goldsmith, Grace A.: The Effectiveness of Acetyl-β-Methylcholine Given by Mouth as a Vasodilating Agent. Ann. Int. Med. **9**: 1196, 1936.

Acetyl-β-methylcholine administered orally to 29 patients in doses of 50 to 1,500 mg. caused an average maximal rise in the temperature of the skin of the digits of 5.82° C. Vasodilation failed to occur in only one case in which an adequate dose was given. The vasodilating effect varies tremendously with different patients, in different pathological conditions, and in the different digits of a given individual. The vasodilation is slow in onset and is of relatively long duration. An adequate dose seems to be between 1,000 and 1,500 mg. No significant changes were produced in blood pressure or pulse rate in the cases studied.

E. A.

Clark, Richard J., Means, James H., and Sprague, Howard B.: Total Thyroidectomy for Heart Disease. New England J. Med. **214**: 277, 1936.

This is a report of the results of total ablation of the thyroid gland in twenty-one cardiac patients operated on at the Massachusetts General Hospital between July, 1933, and May, 1935. Nineteen patients had congestive failure and two had angina pectoris. Conclusions are, therefore, based almost wholly on an experience with congestive failure.

Fifteen patients are now dead. In about one-fourth of the entire series the operation was considered worth while; in three-fourths it was not.

The relatively poor results in the series depended to a considerable degree upon the difficulty in selection of cases and in the fact that too severe cases were originally chosen. The contraindications to operation are numerous, but in cases well selected and handled, worthwhile results were secured, at least temporarily, in 50 per cent.

There is a small group of patients with cardiac failure in whom medical therapy is ineffective in controlling the progressive loss of cardiac reserve for whom total thyroidectomy offers an even chance or worthwhile improvement.

Avoidance of the grosser manifestations of myxedema has not been found difficult. Small daily rations of thyroid usually accomplish this purpose. In some cases, however, at a metabolic level above that of complete myxedema, low rate symptoms have been troublesome.

It is believed that the procedure must be further studied before its usefulness in the treatment of heart disease can be fairly evaluated.

AUTHOR.

Feinberg, Sydney C.: The Treatment of Coronary Artery Disease by Intravenous Injections of Hypertonic Saline Solution. Am. J. M. Sc. **191**: 410, 1936.

Six patients with severe and intractable angina pectoris due to coronary artery disease who were seriously incapacitated and had not improved on rest and customary therapy were treated with repeated intravenous injections of hypertonic saline solution over long periods of time.

Definite and continuous improvement has been noted in their clinical condition.

The hypothesis is presented that the clinical improvement may be due to the fact that the treatment encourages a more rapid development of collateral circulation in the heart wall.

AUTHOR.

Book Reviews

L'Arteriographe des Membres et de L'Aorte Abdominale. By Henri Reboul. Paris, 1935, Masson & Cie. 136 pages, 82 illustrations.

The first half of this monograph on arteriography of the extremities and the aorta is devoted to a survey of the problem, with an historical review and discussions of the use of lipiodol, sodium iodide, uroselectan, l'abrodyl, tenebryl, thorotrast, and collothor. The advantages and disadvantages of each are weighed. The author, apparently, confined his efforts, for the most part, to tenebryl and thorotrast. He considers carefully the fate of thorotrast in the reticulo-endothelium system, and, although this has been a matter of considerable debate in this country, he does not, apparently, feel that it is of sufficient gravity to discourage the use of this substance. Tenebryl (diiodomethane sulphonate of sodium), a substance little used in this country, has been used extensively by Reboul in his cases. He stresses the pressure under which the substance is injected as being of great importance. This point has not been emphasized much in the United States. Pressures of 1,100 to 1,800 gm. are used.

In a chapter on incidents and accidents with arteriography, he reports those of which he has knowledge. They are, for the most part, minor. A few instances of gangrene of the limb are included, but, as most of these cases are potentially gangrenous, one wonders how much the arteriography had to do with the production of gangrene. Dos Santos is quoted as reporting 1,500 injections with only one serious accident, which required ligation of the femoral artery. Recovery followed without gangrene.

The second half of this work consists mainly of plates of arteriographic studies, which are among the finest the reviewer has ever seen. These are accompanied by short case histories, and the following conditions are portrayed: normal arteries, syphilitic arteritis, presenile arteritis, senile arteritis, diabetic arteritis, infectious arteritis, juvenile arteritis (Buerger), Raynaud's disease, Volkmann's syndrome, arterial spasm, aneurisms of various arteries, osteosarcoma, abscesses and tumors of the extremities, and Paget's disease. In addition, there are plates showing arteriographic studies of the aorta in a number of conditions.

One may quarrel with the classification of peripheral vascular disease used by Reboul, but there is no question regarding the value of this monograph to all workers interested in arteriography.

I. S. W.

The Physiology of the Circulation During Puberty. By Gustav Nylin. Acta Medica Scandinavica, Supplementum LXIX, Stockholm, 1935, 51 pages, with diagrams and figures.

This reprint, in German, gives the results of investigations on the various utterances of puberty in girls. Observations on the general development of the body, the changes in the exterior, the variations in standard metabolism, and blood flow and vital capacity were made. Twelve children who were living at the State Institution for the Blind in Stockholm were chosen as far as possible in the stage of development where there was reason to expect that the onset of puberty was imminent.

The reports are divided into three sections: first, growth during puberty; second, standard metabolism; and third, the circulation and vital capacity. Individual diagrams and photographs are included for each subject. The observations were continued over a period of years.

A summary of results relating to the circulation shows that the arteriovenous oxygen difference under standard conditions was remarkably constant during growth; from which it follows that the blood flow is a direct function of standard metabolism. Thus, the minute volume of the heart during the puberty maximum in height growth, like the standard metabolism, was increased somewhat above that corresponding to growth in height and weight.

The pulse rate decreased successively during the whole development and showed no signs of increasing with the onset of puberty.

The gains in stroke volume and heart volume were parallel, and during the puberty maximum exhibited a rapid increase, corresponding to the increase in body surface. The relation between heart volume and stroke volume was constant during development.

The painstaking care with which the observations were made and the duration of time over which they extended should make this a useful contribution to the study of the phenomenon of growth during this period of life. The number of cases is small, however.

H. McC.

LEÇONS DE CARDIOLOGIE faites à l'hôpital Broussais. By Professor Ch. Laubry with the collaboration of Drs. V. Aitoff, Jean Cottet, Ed. Doumer, R. Heim de Balzac, A. Jaubert, J. Lemant, J. Louvel, Georges Marchal, M. Poumailloux, D. Routier, L. Samain, Ad. Van Bogaert, and J. Walser. (Première série.) G. Doin & Cie., Paris, 1936, 245 pages with 79 illustrations.

Professor Laubry and his associates have organized a course in cardiology which consists of three series of lectures given in rotation in successive years, each lecture being given by a member of the staff who has particular interest in the subject under consideration. In this volume we have the lectures given in one year, that is one third of the total "Cours de perfectionnement sur les maladies du coeur et des vaisseaux." The first nine lectures (136 pages) take up the various arrhythmias; the remaining seven lectures deal with water balance, radiology, cyanosis, hematological disturbances in relation to heart disease, recent ideas concerning pathological disturbances of the veins, the bacteriology of endocarditis and rheumatic fever, and the use of sedative medication in heart disease. The lectures are clearly given and well illustrated; the reader should consider them as lectures and should not expect to find references or an index. This volume of lessons is not intended to serve as a complete textbook but should be of interest especially to those who would like to study under well-known French teachers and to those who are interested in teaching.

E. H.

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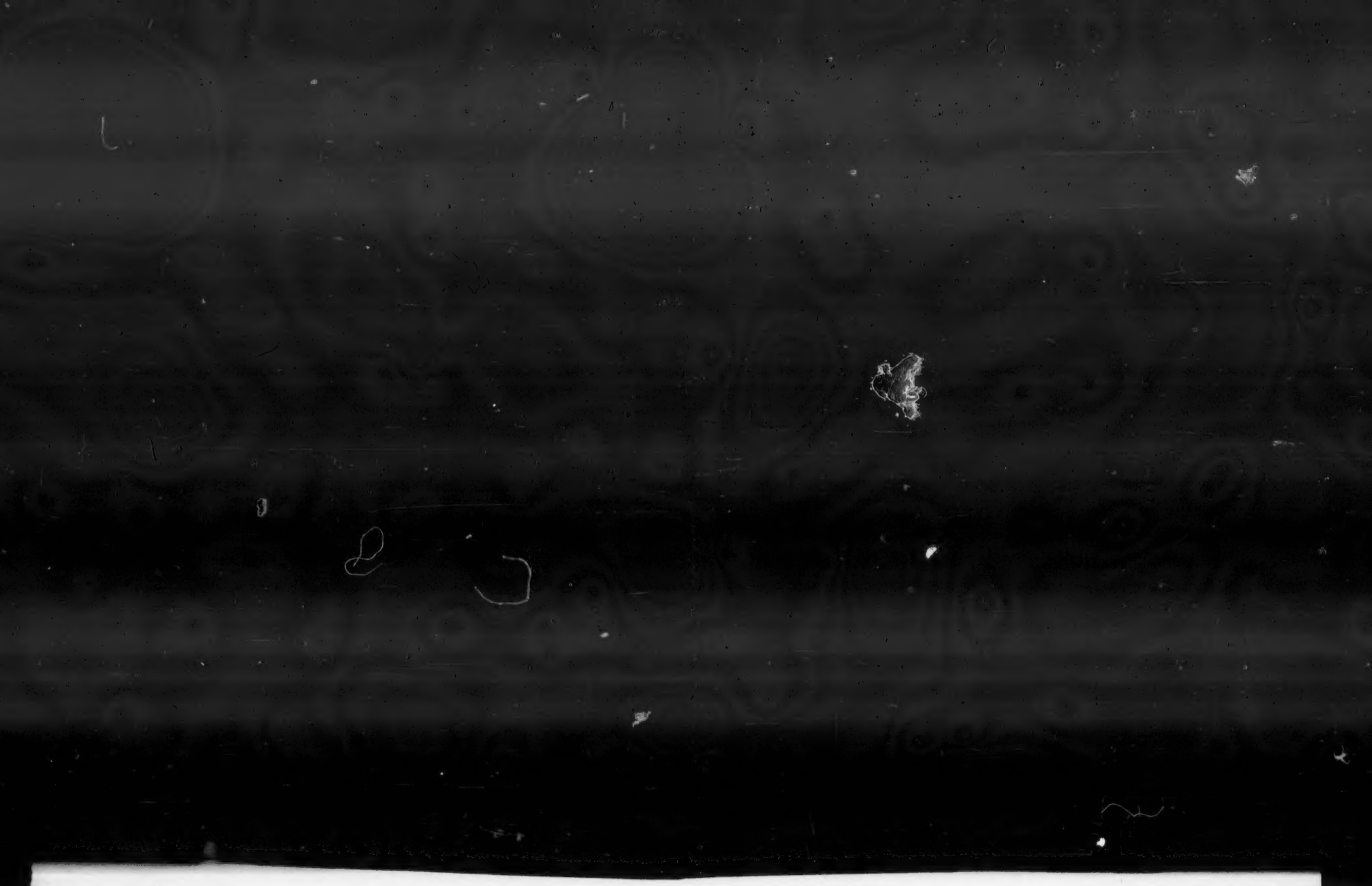
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